Effective Health Care Program

Comparative Effectiveness Review
Number 156

Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

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If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, the EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Contrast-Induced Nephropathy: Comparative Effectiveness of Preventive Measures

Structured Abstract

Objective. To evaluate the comparative effectiveness of interventions (intravenous [IV] fluids, N-acetylcysteine, sodium bicarbonate, and statins, among others) to reduce the risk of contrast-induced nephropathy (CIN), need for renal replacement therapy, mortality, cardiac complications, prolonged length of stay, and other adverse events after receiving low-osmolar contrast media (LOCM) or iso-osmolar contrast media (IOCM).

Data sources. We searched for original published studies in MEDLINE®, Embase®, and the Cochrane Library through July 8, 2015. We also searched ClinicalTrials.gov and the Scopus database.

Methods. Two reviewers independently reviewed each article for eligibility. For each study, one reviewer extracted the data and a second reviewer verified the accuracy. Both reviewers assessed study quality. Together, the reviewers graded the strength of evidence (SOE) on preventing CIN and other adverse outcomes for the comparisons of interest. The team quantitatively pooled results of studies that were sufficiently similar using a random-effects model. We considered a 25-percent relative risk difference to be clinically important.

Results. We found 163 randomized controlled trials (RCTs) and 23 prospective studies of interventions to prevent CIN, including 67 RCTs comparing N-acetylcysteine with IV saline versus IV saline with or without a placebo; 28 RCTs comparing IV sodium bicarbonate versus IV saline; 7 RCTs comparing IV sodium bicarbonate versus N-acetylcysteine plus IV saline; 8 RCTs comparing a statin versus IV saline; 5 RCTs comparing a statin plus N-acetylcysteine versus N-acetylcysteine; 6 RCTs comparing statin versus statin, statin by dose, or statins plus other agents; 5 RCTs comparing an adenosine antagonist versus IV saline; 6 RCTs investigating hemodialysis or hemofiltration versus IV saline; 6 RCTs comparing ascorbic acid versus IV saline, and 3 RCTs comparing ascorbic acid to N-acetylcysteine. Although we found many studies investigating other interventions, the studies were too small and too few to support conclusions regarding the comparative effectiveness of those interventions. The studies were published between 1998 and 2015.

The SOE was low that high-dose [>1,200 mg/day] N-acetylcysteine had a small clinically unimportant effect in preventing CIN when compared with IV saline (pooled risk ratio [RR], 0.78; 95% confidence interval [CI], 0.59 to 1.03); and the SOE was low that low-dose [≤1,200 mg/day] N-acetylcysteine had a borderline clinically important effect in preventing CIN when compared with IV saline (RR, 0.75; 95% CI, 0.63 to 0.89). A sensitivity analysis suggests the effect was clinically important when N-acetylcysteine was given for LOCM (moderate SOE; RR, 0.69; 95% CI, 0.58 to 0.84), but not when it was given for IOCM (low SOE; RR, 1.12; 95% CI, 0.74 to 1.69). Another sensitivity analysis found that the RR estimates did not differ between IV and intra-arterial routes of administration of contrast media. The SOE was low that using a statin plus N-acetylcysteine was more effective than N-acetylcysteine alone in preventing CIN in patients receiving intra-arterial contrast media (RR, 0.52; 95% CI, 0.29 to 0.93), and the SOE was low for a clinically important difference that was not statistically significant when comparing a statin plus IV saline to IV saline alone (RR, 0.68; 95% CI, 0.39 to 1.20). The SOE was low that IV sodium bicarbonate did not differ from IV saline in the risk of CIN (RR, 0.93; 95% CI, 0.68 to 1.27). The SOE was low for a clinically important reduction in CIN that was not statistically significant when comparing IV sodium bicarbonate with IV saline in patients receiving LOCM (RR, 0.65; 95% CI, 0.33 to 1.25). The SOE was low for a clinically important reduction in CIN that was not statistically significant when comparing ascorbic acid with IV saline (RR, 0.72; 95% CI, 0.48 to 1.01). The SOE was low that use of hemodialysis versus IV saline to prevent CIN did not reduce the risk of CIN and may even be harmful (RR, 1.50; 95% CI, 0.56 to 4.04).

Conclusions. The evidence shows a clinically important and statistically significant benefit in studies of three comparisons: low-dose N-acetylcysteine compared with IV saline, N-acetylcysteine compared with IV saline in patients receiving LOCM, and statins plus N-acetylcysteine compared with N-acetylcysteine alone in patients receiving intra-arterial contrast media. Future research is needed to determine whether statins can reduce CIN in patients receiving IV contrast media, and to further define specific contexts in which patients could benefit from use of N-acetylcysteine.

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Executive Summary

Background

The administration of iodinated contrast media is an essential component of many diagnostic and therapeutic procedures that involve radiologic imaging. One important potential side effect of iodinated contrast administration is contrast-induced nephropathy (CIN), defined as an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology.[1] This definition of CIN is the one most commonly used in the past in studies examining the risk, prevention, and treatment of CIN. More recent definitions of acute kidney injury have not yet been used extensively in the CIN literature.

The precise mechanism of CIN is not entirely understood. The leading theories are that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of the contrast media.[2,3] Some experts have questioned whether acute kidney injury occurring after intravascular administration of contrast media is caused by coexisting risk factors and only coincidentally related to the contrast media, especially if contrast media are administered through the intravenous route (IV).[4] Regardless of the precise etiology, however, the development of acute kidney injury after use of intravascular contrast media remains a major concern for clinicians.

Clinicians often worry about the possibility that intravascular administration of contrast media could lead to acute or chronic kidney failure. The reported incidence of CIN varies, but it is a leading cause of hospital-acquired kidney failure.[5] Although renal function returns to normal in most patients, the acute kidney injury may require renal replacement therapy or lead to chronic kidney disease (CKD) in a small proportion of patients who develop CIN. Because of increasing use of contrast media in radiologic and cardiologic procedures, and the increasing prevalence of populations vulnerable to CIN (i.e., people having CKD, diabetes mellitus, or hypertension, as well as the elderly), kidney failure due to CIN is a substantial concern.

Numerous strategies have been used to try to prevent CIN. These strategies include oral hydration; volume expansion with sodium chloride or bicarbonate or a combination of both; administration of N-acetylcysteine; withdrawal of metformin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or nonsteroidal anti-inflammatory drugs; hemofiltration or hemodialysis; statins; use of low-osmolar or iso-osmolar nonionic contrast media; and reducing the volume of contrast media administered. Despite these varied strategies, no clear consensus exists in clinical practice about the most effective intervention to prevent or reduce CIN. We therefore sought to perform a comprehensive systematic review of the effectiveness of different measures for preventing CIN.

We also sought to determine whether the risk of CIN, and therefore the need for preventive measures, varies according to route of administration, type of contrast media, or patient characteristics. Intra-arterial procedures are thought to carry the highest risk of CIN, and therefore most of the studies are in the population undergoing these procedures, while the need for preventive strategies for patients undergoing IV procedures is more controversial. To better understand the results, we separately analyze patients who received IV versus intra-arterial contrast media, as these groups may have different risk profiles and susceptibility to CIN. We also performed a separate analysis for patients receiving iso-osmolar contrast media (IOCM) or low-osmolar contrast media (LOCM), the two types of contrast media in regular clinical use today in the United States. Finally, preventive measures may be more effective in patients at higher risk of CIN, so we analyzed data by baseline risk when possible.

Key Question

In patients undergoing imaging studies requiring intravenous (IV) or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy for the outcomes of incidence of contrast-induced nephropathy, chronic kidney disease, end stage renal disease, mortality, and other adverse events?

a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate, or creatinine level)?

b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used (i.e., low-osmolar contrast media vs. iso-osmolar contrast media)?

c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?

Data Sources

We searched the following databases for primary studies published through July 8, 2015: MEDLINE®, Embase®, and the Cochrane Library. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. We also searched ClinicalTrials.gov to identify ongoing studies. We searched for publicly available data held by the U.S. Food and Drug Administration.

Study Eligibility Criteria, Participants, and Interventions

We followed the population, interventions, comparators, outcomes, timing, and setting (PICOTS) framework in developing the criteria for including studies in the review, and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We included randomized controlled trials (RCTs) of any intervention to prevent CIN (including administration of N-acetylcysteine, sodium bicarbonate solution, sodium chloride solution, statins, adenosine antagonists, diuretics, vasoactive drugs, antioxidants, dopamine, and renal replacement therapy) in which the study groups received either IOCM or LOCM via IV or intra-arterial injection. Studies had to report on at least one of the outcomes listed in the Key Question. We included observational studies where available for all comparisons of interest.

Study Appraisal and Synthesis Methods

The titles and abstracts were independently screened by two reviewers. Inclusion at the title-screening level was liberal; if a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team. At random intervals during screening, senior team members performed quality checks to ensure that eligibility criteria were applied consistently.

We performed de novo meta-analyses of all studies on a given comparison if the studies were similar by qualitative or statistical criteria. Pooled risks for large comparisons (18 or more studies) were calculated using a random-effects model using the method of DerSimonian and Laird.[6] For comparisons with fewer than 18 studies, we used the Knapp-Hartung small sample estimator approach. This method allows for small sample adjustments to the variance estimates and forms confidence intervals (CI) based on the *t* distribution with $k - 1$ degrees of freedom.[7] Statistical heterogeneity was assessed using the I-squared statistic.

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies:[8]

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing. Study limitations were determined for each comparison group for CIN and other reported outcomes. Study limitations were determined using the following algorithm for a body of evidence. A body of evidence was assessed as having high study limitations if greater than 50 percent of the studies scored negative in one or more of the criteria. A body of evidence was assessed as having low study limitations if most (51% or greater) of the studies scored positive in all five domains. Bodies of evidence not meeting one of the above criteria were assessed as having medium study limitations.

The team graded the strength of evidence (SOE) on comparisons of interest for the key outcomes. We used the grading scheme recommended in the Agency for Healthcare Research and Quality *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[9] and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[9]

Following the guidance of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group,[10] we rated evidence as precise if the total number of patients exceeded an optimum information size and the 95% (CI) excluded a risk ratio of 1.0. If the total number of patients exceeded the optimum information size and the 95% CI did not exclude the possibility of no difference (i.e., risk ratio of 1.0), we rated the evidence as precise only if the 95% CI excluded the possibility of a clinically important benefit or harm (i.e., risk ratio less than 0.75 or greater than 1.25). For the main outcome of interest, CIN, we used an optimum information size of 2,000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative risk difference of 25 percent. For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative risk difference of 25 percent. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. We classified the SOE pertaining to each comparison into four category grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and it was subsequently downgraded for each domain in which a problem was identified. If the magnitude of effect was very large, the SOE could be upgraded.

Observational studies were considered in grading the strength of a body of evidence if the overall results of the observational studies were not similar to the RCTs applicable to the comparison.

Organization of This Report

The following Results section reports on a number of comparisons. We report in detail on comparisons for which substantial evidence exists, starting with the comparisons that have received the most attention in the literature (N-acetylcysteine plus IV saline vs. IV saline, IV sodium bicarbonate vs. IV saline, N-acetylcysteine plus IV saline vs. IV sodium bicarbonate, statins plus IV saline vs. IV saline, adenosine antagonists plus IV saline vs. IV saline, renal replacement therapy vs. IV saline, and ascorbic acid plus IV saline vs. IV saline). At the end of the results section, we refer to information about other miscellaneous comparisons for which there were too few studies to draw any conclusions. Details on those comparisons appear in Appendixes H and I of the full report.

Results

The literature search revealed a total of 186 articles: 163 RCTs and 23 observational studies on interventions for preventing CIN, including 67 RCTs (N = 13,176) on N-acetylcysteine versus IV saline; 28 RCTs (N = 6,645) on IV sodium bicarbonate versus IV saline; 7 RCTs (N = 1,688) on N-acetylcysteine versus sodium bicarbonate; 19 RCTs (N = 10,574) on statins (8 comparing a statin to IV saline, 5 comparing a statin plus N-acetylcysteine to N-acetylcysteine, and 6 other comparisons of statin versus statin, statin by dose, or statins plus other agents); 5 RCTs (N = 3,647) on adenosine antagonists; 6 RCTs (N = 790) on use of hemodialysis or hemofiltration to prevent CIN; and 8 RCTs (N = 1,830) comparing ascorbic acid to IV saline (N = 6) or N-acetylcysteine (N = 3).

We included in the meta-analyses 54 RCTs investigating N-acetylcysteine with IV saline versus IV saline with or without a placebo (46 studies using only intra-arterial contrast media, 7 studies using IV contrast media, and 1 study that did not report the route of administration); 19 RCTs investigating the use of sodium bicarbonate versus IV saline (14 studies using only intra-arterial contrast media, 2 studies using only IV contrast media, and 3 studies using either intra-arterial or IV contrast media); 7 RCTs investigating use of IV sodium bicarbonate versus N-acetylcysteine plus IV saline (6 studies using intra-arterial contrast media and 1 study using IV contrast media); 8 RCTs investigating use of a statin versus a placebo or IV saline (all studies using intra-arterial contrast media); 5 RCTs investigating the use of a statin plus N-acetylcysteine versus N-acetylcysteine alone (all studies using intra-arterial contrast media); 3 RCTs investigating use of hemodialysis versus IV saline alone (all studies using intra-arterial contrast media, 1 of which also included some patients receiving IV contrast media); 4 RCTs investigating use of an adenosine antagonist with IV saline versus IV saline alone (3 studies using intra-arterial contrast media and 1 study using IV contrast media); 6 studies investigating the use of ascorbic acid versus IV saline (all studies using intra-arterial contrast media); and 3 studies investigating the use of ascorbic acid versus N-acetylcysteine (all studies using intra-arterial contrast media). The results of these studies were published between 1998 and 2015.

N-Acetylcysteine Versus IV Saline

Using a random-effects model to pool studies comparing N-acetylcysteine with IV saline versus IV saline with or without a placebo, the pooled risk ratio for CIN was 0.78 (95% CI, 0.59 to 1.03) for high-dose N-acetylcysteine (>1,200 mg/day), indicating a small effect that is clinically unimportant and statistically insignificant (p=0.075) with low SOE, and 0.75 (95% CI, 0.63 to 0.89) for low-dose N-acetylcysteine (1,200 mg/day or less), indicating a borderline clinically important effect. Sensitivity analyses revealed imprecise estimates of the pooled risk ratio for CIN when stratified by route of administration of contrast media: 0.78 (95% CI, 0.55 to 1.12) for high-dose N-acetylcysteine when intra-arterial contrast media were used (high-dose N-acetylcysteine with intra-arterial contrast media administration pooled risk ratio was run with Knapp-Hartung method); 0.55 (95% CI, 0.12 to 2.62) for high-dose N-acetylcysteine when IV contrast media were used; 0.77 (95% CI, 0.66 to 0.91) for low-dose N-acetylcysteine when intra-arterial contrast media were used; and 0.62 (95% CI, 0.18 to 2.10) for low-dose N-acetylcysteine when IV contrast media were used (low-dose N-acetylcysteine with IV contrast media administration pooled risk ratio was run with Knapp-Hartung method). The pooled risk ratio was 0.69 (95% CI, 0.58 to 0.84) for N-acetylcysteine when LOCM was used, suggesting a clinically important benefit, and 1.12 (95% CI, 0.74 to 1.69) for N-acetylcysteine when IOCM was used. When we examined how the risk ratio estimates varied according to baseline characteristics of the study population, we did not observe any meaningful difference by age, baseline renal function, presence or absence of diabetes mellitus, or proportion of female patients. When we examined how results of studies of N-acetylcysteine varied in forest plots organized by the number of study limitations, we did not see any pattern indicative of a trend by study quality. The SOE was low for all of the N-acetylcysteine versus IV saline comparisons except in the case of administration of N-acetylcysteine and LOCM, the SOE was moderate.

The SOE was low that N-acetylcysteine with IV saline did not differ from IV saline with or without a placebo in the need for renal replacement therapy, cardiac events, or length of hospitalization. Most of the studies addressing these outcomes had important study limitations (frequently lacking documentation of allocation concealment or blinding of participants and personnel) and were consistent but imprecise. We found insufficient evidence to draw conclusions about the effect of N-acetylcysteine on mortality. The results of observational studies were similar to the RCTs.

IV Sodium Bicarbonate Versus IV Saline

Using a random-effects model for studies comparing IV sodium bicarbonate versus IV saline, the overall pooled risk ratio of CIN was 0.93 (95% CI, 0.68 to 1.27). The point estimate of the risk ratio indicated a clinically unimportant difference in the risk of CIN. The associated CI ruled out a clinically important increase in CIN but did not rule out the possibility of a clinically important decrease in CIN. However, IV sodium bicarbonate was more effective than IV saline in preventing CIN (pooled risk ratio, 0.65; 95% CI, 0.33 to 1.25), with a clinically important benefit when given for studies with LOCM only, but not when given for studies with IOCM (pooled risk ratio, 1.02; 95% CI, 0.70 to 1.48). The analysis for LOCM and IOCM subgroups was completed with the Knapp-Hartung method. The SOE was low for this conclusion because most of the studies had important study limitations (frequently lacking documentation of allocation concealment or blinding of participants and personnel) and inconsistent results.

The SOE also was low that IV sodium bicarbonate did not differ from IV saline in mortality or the need for renal replacement therapy. Most of the studies addressing these outcomes had at least one important study limitation (frequently lacking blinding of participants and personnel) and were consistent but imprecise. We found insufficient evidence to draw conclusions about how IV sodium bicarbonate compared with IV saline in the risk of cardiac events and length of hospitalization. Two observational studies reported a beneficial effect of sodium bicarbonate in reducing CIN.

N-Acetylcysteine Versus Sodium Bicarbonate

In the RCTs comparing IV sodium bicarbonate with the combination of N-acetylcysteine and IV normal saline, using the Knapp-Hartung method, the pooled risk ratio for CIN was 1.11, indicating no clinically important difference, and the studies were inconsistent and the 95% CI was so wide (0.51 to 2.41) that we cannot rule out the possibility of either an important decrease or important increase in risk of CIN. Therefore, the SOE was insufficient to support a conclusion about the comparative effectiveness of these two interventions. The evidence also was insufficient to draw conclusions about potential differences between the two interventions in mortality, cardiac events, need for renal replacement therapy, or length of hospitalization. Two observational studies compared N-acetylcysteine to sodium bicarbonate. One showed no difference between interventions, and the other showed a higher incidence of CIN in patients receiving sodium bicarbonate alone.

Statins

The SOE was low in studies that compared use of a statin plus IV fluids versus IV fluids alone, showing a clinically important reduction in CIN with statin use that was not statistically significant (pooled risk ratio, 0.68; 95% CI, 0.39 to 1.20). Because of the small number of studies, the pooled risk ratio was determined with the Knapp-Hartung method. Eight studies with a total population of 5,024 were included to reach this conclusion; five studies included only patients with CKD, three included patients with cardiac issues, three included patients with diabetes, and one study included participants from the general patient population. Half of these studies had at least one important limitation (in allocation concealment or blinding of participants and personnel) but were designed to measure CIN as the primary outcome and consistently showed a benefit in reducing CIN in favor of the statin drug, with relatively precise estimates. The number needed to treat was higher for statins than for high-dose N-acetylcysteine despite having a lower pooled risk ratio estimate because of differences between the two groups of studies in the baseline risk of CIN.

The SOE was insufficient that mortality, the need for renal replacement therapy, cardiac events, and hospital length of stay did not differ between statins plus IV fluids versus IV fluids alone. Most of the studies addressing these outcomes had at least one important study limitation and were consistent but imprecise. One observational study showed results similar to the RCTs.

The pooled estimate of the risk ratio for statins plus N-acetylcysteine versus N-acetylcysteine alone was both statistically significant and clinically important (pooled risk ratio, 0.52; 95% CI, 0.29 to 0.93), with a number needed to treat of 18 (95% CI, 13.44 to 34.72). The pooled risk ratio for statins plus N-acetylcysteine versus N-acetylcysteine was also calculated with the Knapp-Hartung method. Three studies included CKD patients, two included patients with cardiac issues, and one had a general population. The CI was wide enough that a clinically unimportant difference cannot be ruled out. The SOE was low and was limited by the imprecision of the studies.

The SOE was insufficient that mortality, the need for renal replacement therapy, cardiac events, and hospital length of stay did not differ between statins plus N-acetylcysteine versus N-acetylcysteine alone. Most of the studies addressing these outcomes had at least one important study limitation and were consistent but imprecise.

Adenosine Antagonists

The SOE was insufficient when studies compared adenosine antagonists plus IV saline versus IV saline alone because the CI was so wide that we could not rule out either a clinically important decrease or a clinically important increase in CIN (pooled risk ratio, 0.80; 95% CI, 0.01 to 44.48). The SOE was insufficient to make conclusions about the impact of adenosine antagonists on the need for renal replacement therapy, cardiac events, mortality, or length of hospitalization.

Renal Replacement Therapy

The pooled analysis for the three studies of hemodialysis compared with IV saline yielded a pooled risk ratio of 1.50, which is consistent with a clinically important increased risk of CIN. The corresponding 95% CI was 0.56 to 4.04, which is consistent with either an increased risk or no important difference. Although the studies on hemodialysis had high risk of bias, the results were consistent enough and precise enough to provide low SOE that hemodialysis does not reduce the risk of CIN when compared with IV saline. Two RCTs compared hemofiltration to IV saline and reported that patients with severe CKD may have a lower incidence of CIN with hemofiltration, but the SOE was insufficient to support a conclusion. The SOE was insufficient to make conclusions about the impact of using hemodialysis or hemofiltration on mortality, cardiac events, the need for subsequent renal replacement therapy, or the length of hospitalization.

Ascorbic Acid

From studies of the effect of ascorbic acid plus IV fluids compared with IV fluids alone, the pooled risk ratio was 0.72 (95% CI, 0.48 to 1.01), indicating a clinically important effect that was not statistically significant. The pooled estimate of the effect of ascorbic acid compared with N-acetylcysteine demonstrated a clinically unimportant reduced risk of CIN with ascorbic acid use that was associated with a wide CI (pooled risk ratio, 0.89; 95% CI, 0.34 to 2.30). The SOE was low for both comparisons.

Other Comparisons

Although we found many studies investigating other interventions (Table A), the evidence generally was insufficient to support conclusions regarding their comparative effectiveness.

Table A. Miscellaneous comparisons for which evidence was insufficient

Intervention	Comparisons
N-acetylcysteine	Dialysis, ascorbic acid, nebivolol, atorvastatin, aminophylline, theophylline, fenoldopam, misoprostol
IV sodium bicarbonate	Acetazolamide, long-term vs. short-term IV sodium bicarbonate, IV saline in 5% dextrose, oral sodium bicarbonate
N-acetylcysteine plus IV sodium bicarbonate	IV saline and N-acetylcysteine, furosemide plus saline plus N-acetylcysteine, placebo plus sodium bicarbonate, sodium bicarbonate
Diuretics (furosemide, mannitol, and acetazolamide)	IV saline
Vasoactive agents (fenoldopam, calcium antagonists, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers)	IV saline
Antioxidants (probucol, pentoxifylline)	Different hydration regimens
Fluid administration (various)	Fluid administration (various)
Dopamine (or dopamine plus furosemide)	Dopamine, furosemide, mannitol, IV saline

Discussion

Numerous interventions have been used in studies to reduce the risk of CIN. The greatest reduction in CIN was seen with N-acetylcysteine in patients receiving LOCM (Low SOE), and with statins plus N-acetylcysteine (Low SOE). All of the studies included in the statin meta-analyses were of patients receiving intra-arterial contrast media, so no evidence exists on the potential benefit of statins in patients receiving IV contrast media. In the analysis of N-acetylcysteine plus IV saline compared with IV saline alone, there is also evidence of a clinically important reduction in CIN when N-acetylcysteine plus IV saline was compared with IV saline alone in patients receiving LOCM (low SOE). One study has questioned whether N-acetylcysteine is effective at preventing CIN or if it simply reduces serum creatinine.[11] This is an important finding; however, the reduction in serum creatinine reported as significant was measured at 4 hours, and it was insignificant at 48 hours, which was the timeframe for the measure of CIN in this report. IV sodium bicarbonate did not appear to be any more effective than IV saline (low SOE). However, a clinically important reduction in CIN was seen when sodium bicarbonate with IV saline was compared with IV saline in studies using LOCM. Ascorbic acid plus IV saline had a clinically important but statistically insignificant effect compared with IV saline alone (low SOE). For other interventions and comparisons included in this report, the SOE was insufficient to support a definite conclusion because, in general, the studies had important limitations, the comparators varied too much, the effects were inconsistent and imprecise, and the magnitude of effect was weak. Although usual care often involves administration of IV fluids, the evidence was insufficient to support a conclusion about the relative effectiveness of IV versus oral fluids, or whether fluids should be given before or after the procedure.

Despite the large body of evidence on N-acetylcysteine, the SOE was low, primarily because of limitations in the quality of many of the studies and inconsistency in results across studies, with the possibility of an effect too small to be clinically meaningful. The low SOE helps to explain why N-acetylcysteine is not used more often in clinical practice and why professional organizations offer differing recommendations about the use of N-acetylcysteine to prevent CIN. The joint American College of Cardiology/American Heart Association 2012 guideline recommends against use of N-acetylcysteine for patients receiving intra-arterial contrast in cardiac procedures.[12] In comparison, the 2012 Kidney Disease: Improving Global Outcomes

(KDIGO) Clinical Practice Guideline for Acute Kidney Injury suggests using oral N-acetylcysteine with IV fluids in patients at increased risk for CIN, while acknowledging that the quality of evidence is very low.[13] Although N-acetylcysteine is inexpensive and appears to be safe, the evidence may not be strong enough to support a firm policy of routine use, especially in the absence of stronger evidence on clinical outcomes other than the incidence of CIN.

For clinicians who want to reduce the risk of CIN in patients receiving LOCM or IOCM, evidence of potential benefit was seen with use of a statin plus N-acetylcysteine compared with N-acetylcysteine alone. The aggregate risk ratio was 0.52, suggesting a nearly 50 percent relative reduction in risk of CIN, but the SOE was low. Despite previous systematic reviews highlighting the existence of this evidence on the effectiveness of statins in lowering the risk of CIN, statins are not used routinely in clinical practice to prevent CIN. Furthermore, we are not aware of any professional guidelines recommending their use for this indication. It is possible that the findings reported in the studies of statins could be partly explained by a direct effect of statins on glomerular filtration rate that is independent of a protective effect on kidney function, as has been reported in one study.[14] However, with increasing recognition of the beneficial cholesterol-independent vascular effects of statins, it may be time to reassess the role of statins in preventing CIN, especially since statins are readily available, easy to administer, and relatively inexpensive.

Our primary analysis showed that IV sodium bicarbonate did not produce a clinically important decrease in CIN compared with IV saline, contrary to the conclusion of a recent meta-analysis.[15] This difference in conclusions can be attributed to the fact that the other meta-analysis included five studies that used a combination of IV sodium bicarbonate and N-acetylcysteine, which we excluded from our analysis of the effects of sodium bicarbonate. In a sensitivity analysis, we found low SOE for a clinically important benefit in decreasing CIN when sodium bicarbonate was used in studies with LOCM, but the difference was not statistically significant. This finding suggests that IV sodium bicarbonate could have a role in preventing CIN, but only in patients receiving LOCM.

Future Research

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to their baseline risk of CIN, especially since it may be difficult to detect a treatment effect in patients having a low risk of CIN. Patients with normal or near-normal serum creatinine may have a lower risk for developing CIN than those with higher serum creatinine levels. Also, patients with risk factors for CKD have a higher risk of developing CIN than patients without such risk factors. Unfortunately, we had a limited ability to stratify the analysis according to baseline risk because almost all studies had a mixed patient population and did not report the results separately by baseline risk.

More research could help to strengthen the evidence about whether N-acetylcysteine or IV sodium bicarbonate would be beneficial in a particular clinical context, such as patients with an increased risk of developing CIN who will be receiving LOCM. Given the evidence from our primary analysis showing that IV sodium bicarbonate did not produce a clinically important reduction in CIN compared with IV saline and did not differ in head-to-head comparisons with N-acetylcysteine, it may be difficult to justify additional RCTs of IV sodium bicarbonate unless they focus on particular groups of patients having a higher risk of developing CIN.

The clinically important benefit of statins demonstrated in this analysis provides a rationale for further studies investigating whether the effect differs by statin dose, timing of administration, type of contrast media, or baseline risk of the patient population. Further investigation into the findings on statins versus IV saline could be performed through examination of the possible effect of risk modifiers, such as baseline kidney function, concurrent use of nephrotoxic medications, and patient demographics. Future studies could explore the effect of statins on reducing CIN when contrast media are administered intravenously. In addition, studies could be done in individuals without cardiovascular risk factors to determine whether the effectiveness of statin therapy in reducing CIN occurs in the absence of the physiologic effects of statins on coexisting cardiovascular disease.

Little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies with IV contrast media. If oral hydration were shown to be as effective as IV saline, it would be a simple and potentially cost-effective strategy for preventing CIN. Unfortunately, very few studies investigated oral hydration versus IV saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus IV saline, especially for intra-arterial contrast procedures such as coronary angiography.

Finally, it is very difficult to apply the existing evidence to patients receiving IV contrast media because the vast majority of studies focused on patients receiving intra-arterial contrast media. The risk of CIN may be low enough with the IV administration of LOCM and IOCM to make it very difficult to demonstrate the effectiveness of an intervention for preventing CIN. To determine the effectiveness of interventions for preventing CIN in patients receiving IV contrast media, it may be necessary to perform large studies of patients having a high risk for developing CKD.

Regardless of which populations or interventions are involved, it is important that future studies use an accepted definition of CIN and report outcomes beyond CIN that are important to patients. Critical for future studies is more standardized reporting on adverse outcomes, such as drug side effects, need for hemodialysis, length of hospitalization, quality of life, and mortality.

To develop more effective interventions for preventing CIN, it may be necessary to conduct additional research on the pathophysiological mechanisms by which contrast media may contribute to acute kidney injury. It would be important to differentiate the direct effects of contrast media from other factors that can contribute to acute kidney injury in patients receiving IV or intra-arterial contrast media.

Conclusions

From all the studies of interventions to reduce the risk of CIN, the evidence only shows a clinically important and statistically significant benefit in studies of three comparisons: low-dose N-acetylcysteine compared with IV saline, N-acetylcysteine compared with IV saline in patients receiving LOCM, and statins plus N-acetylcysteine compared with N-acetylcysteine alone in patients receiving intra-arterial contrast media. Additional research is needed to determine whether statins can reduce CIN in patients receiving IV contrast media, and to further define specific contexts in which patients could benefit from use of N-acetylcysteine.

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Introduction

Background

The administration of iodinated contrast media is an essential component of a number of diagnostic and therapeutic procedures that involve radiologic imaging. One important potential side-effect of iodinated contrast administration is contrast-induced nephropathy (CIN, see Appendix A for a list of acronyms), defined as an increase in serum creatinine of more than 25 percent or 0.5 mg/dL within 3 days of intravascular administration of contrast media in the absence of an alternative etiology.[1] This definition of CIN, or variations of it, is the one most commonly used in the past by studies examining the risk, prevention, and treatment of CIN. More recent consensus definitions of acute kidney injury, such as RIFLE[2] and AKIN,[3] have not yet been used extensively in the CIN literature. Although some guidelines have employed the term "contrast-induced acute kidney injury" (CI-AKI) instead of CIN, the vast majority of the literature has used the older term, CIN, so we will use the older term in our report.

The precise mechanism of CIN is not entirely understood. The leading theories are that CIN results from hypoxic injury of the renal tubules induced by renal vasoconstriction or by direct cytotoxic effects of the contrast media.[4,5] Some experts have questioned whether acute kidney injury occurring after intravascular administration of contrast media is caused by co-existing risk factors and only coincidentally related to the contrast media, especially if contrast media are administered by the intravenous (IV) route. In a meta-analysis, McDonald et al., 2013 concluded that the incidence of acute kidney injury was similar between patients receiving IV contrast media and patients receiving an imaging procedure without contrast media. Regardless of the precise etiology, however, the development of acute kidney injury after use of intravascular contrast media remains a major concern for clinicians.[6]

Clinicians often worry about the possibility that intra-vascular administration of contrast media in diagnostic or therapeutic procedures could lead to acute or chronic kidney failure. Indeed, CIN is cited as a leading cause of hospital-acquired kidney failure.[7] Although renal function returns to normal in most patients, acute kidney injury may require short-term renal replacement therapy or may lead to chronic kidney disease and a need for long-term renal replacement therapy. Clinicians are concerned about the risk of CIN because of increasing use of contrast media in radiologic and cardiologic procedures, and the high prevalence of populations vulnerable to CIN (i.e., people having chronic kidney disease, diabetes mellitus, or hypertension, as well as the elderly). Various types of imaging studies or procedures use IV or intra-arterial contrast media, including: IV pyelograms; brain, head and neck, body, or coronary computed tomograms (CT); cerebral, cardiac, or peripheral vascular angiograms; and radiologic therapeutic procedures. Contrast media is injected intravenously for CT and intra-arterially for angiograms and related interventional procedures. More than 62 million CT studies were performed in the United States in 2006 and the use of CT tripled between 1996 and 2010, from 52 studies per 1000 patients to 149 studies per 1000 patients.[8]

The reported incidence of CIN varies, but a reasonable overall estimate is that it occurs in about 2 percent of patients receiving intra-vascular contrast media.[7] Variation in the populations studied makes it difficult to determine whether the incidence of CIN has increased over time. Most of the estimates are derived from invasive angiographic studies, over the last few decades, using intra-arterial contrast media, which may have a higher risk of CIN than imaging studies using IV contrast media. One problem in determining the precise incidence of CIN is that many patients do not remain hospitalized for enough time after contrast administration to make the diagnosis. In addition, the use of serum creatinine as a marker of renal function has its limitations. It is often difficult to exclude other possible etiologies of elevations in serum creatinine. Furthermore, the incidence may vary according to the osmolality of contrast media used. Although there is consensus that the risk of CIN is highest with high-osmolar contrast media (HOCM), which has an osmolality five to eight times higher than plasma osmolality, HOCM is no longer used in clinical practice. It is unclear whether or not the risk of CIN differs between low-osmolar contrast media (LOCM), which has an osmolality two to three times plasma osmolality, and iso-osmolar contrast media (IOCM), which is isotonic to plasma. It is also often difficult to distinguish the effects of contrast media from the effects of physiologic confounders that could elevate the serum creatinine in patients undergoing radiologic studies. For example, blood flow to the kidneys could be compromised by emboli or vascular compression from catheter manipulation.[9,10] Nevertheless, it is important to carefully examine the evidence on the effectiveness of interventions for preventing CIN while taking into consideration how the effectiveness may depend on factors such as the route of administration or the type of contrast media being used.

Numerous strategies to prevent CIN have been used, including: oral fluids; volume expansion with sodium chloride, sodium bicarbonate, or a combination of both; administration of N-acetylcysteine, statins, angiotensin converting enzyme inhibitors, or angiotensin II receptor blockers; withdrawal of nonsteroidal anti-inflammatory drugs; and hemofiltration or hemodialysis. Withdrawal of metformin does not prevent CIN; it is discontinued before use of contrast because acute kidney injury may lead to metformin-associated lactic acidosis. Recent meta-analyses on the prevention of CIN have yielded contradictory results. A meta-analysis by Sun et al., 2013 concluded that the evidence on use of IV N-acetylcysteine to prevent CIN was too inconsistent to determine the efficacy.[11] Another meta-analysis, performed by Loomba et al., 2014,[12] concluded that N-acetylcysteine may help to prevent CIN in patients undergoing coronary angiography, but does not have any impact on clinical outcomes such as need for dialysis or mortality. A meta-analysis by Xie et al., 2014[13] concluded that statins given before angiography are effective in preventing CIN, but the optimum dose and duration for statin use are unknown. A recent review of randomized controlled trials (RCTs) of sodium bicarbonate administration for prevention of CIN revealed the conflicting nature of the evidence, with some studies showing benefit and others showing no benefit.[14]

Despite the number of previous reviews, uncertainty persists about several issues, including:

1. The efficacy of oral fluids versus IV fluids in preventing CIN;[15,16]
2. The optimal timing (pre- versus post-contrast media administration or both), duration, and type of IV fluids used to prevent CIN[17];
3. The efficacy of low versus high-dose N-acetylcysteine;
4. The efficacy of a combination of interventions, such as N-acetylcysteine plus sodium bicarbonate;
5. The efficacy of statins, taking into consideration dose and duration of the medication;
6. The efficacy of vasoactive drugs;
7. The efficacy of hemodialysis and hemofiltration relative to the invasive nature and cost of these interventions;
8. Whether any intervention is needed for IV contrast media procedures when there is uncertainty about whether IV contrast media is associated with CIN; and
9. Effect of the volume of contrast media administered, and the possibility of preventing CIN by keeping the volume of contrast media below a threshold.

Guidelines around contrast media administration have been published by a number of organizations. The 2007 American College of Radiology practice guideline focused on the correct administration of contrast media and the patients who are most likely to benefit from using LOCM instead of HOCM, rather than the evidence for or against different preventive measures. Guidelines on the prevention of CIN were published in 2007 by the Canadian Association of Radiologists,[19] and they were published following what they described as an "in-depth literature search with critical review"; however, no further details were included about the methods. Guidelines were also issued in 2006 by the CIN Consensus Working Panel, an international multidisciplinary group; these guidelines were based on an evidence review through 2005.[20] One section of the 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury specifically addressed contrast-induced acute kidney injury. The method of synthesis varied among these guidelines and many were based on literature review and consensus opinions of clinical experts.[21]

In light of the increasing use of contrast media in radiologic and cardiologic procedures, the high prevalence of populations vulnerable to CIN (e.g., people having chronic kidney disease, diabetes mellitus, or hypertension as well as the elderly), and discrepant results from prior analyses, we sought to perform a comprehensive systematic review of this topic for the benefit of clinicians who wish to prevent CIN in patients undergoing imaging studies.

Scope of the Review

We reviewed studies that assess the effectiveness of one or more measures for preventing CIN in patients receiving either IOCM or LOCM, the two types of contrast media still in regular use in the United States (Figure 1 and Table 1). We included studies that reported on specific short-term or long-term outcomes (Table 2). When studies allowed, separate results for CIN prevention were reported for intra-arterial compared to IV contrast.

Key Question

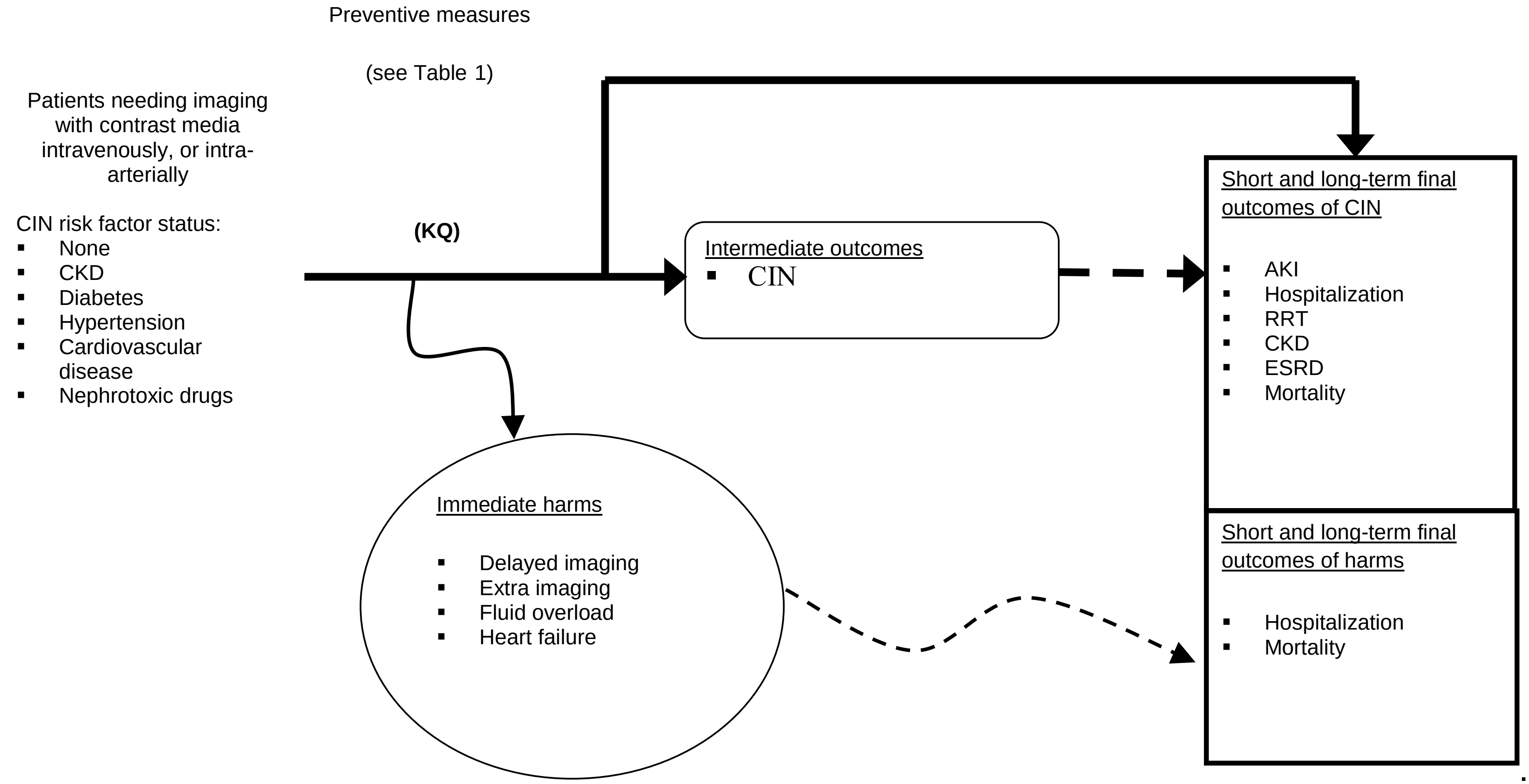
In patients undergoing imaging studies requiring intravenous (IV) or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy for the outcomes of incidence of contrast-induced nephropathy, chronic kidney disease, end stage renal disease, mortality, and other adverse events?

a. How does the comparative effectiveness of prevention measures vary by patient characteristics (known risk factors such as age, comorbidity, glomerular filtration rate, or creatinine level)?

b. How does the comparative effectiveness of prevention measures vary according to the type of contrast media used (i.e., low-osmolar contrast media vs. iso-osmolar contrast media)?

c. How does the comparative effectiveness of prevention measures vary by characteristics of the interventions (e.g., dose, duration, and timing)?

Figure 1. Analytic framework comparing the benefits and harms of different methods used to prevent contrast-induced nephropathy in patients receiving low-osmolar or iso-osmolar contrast media



AKI=acute kidney injury; CIN=contrast induces nephropathy; CKD=chronic kidney disease; ESRD=end stage renal disease; IOCM=iso-osmolar contrast media; KQ=Key Question; LOCM=low-osmolar contrast media; RRT=renal replacement therapy

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for defining the scope of the review

Populations	• All adults and children undergoing procedures requiring low-osmolar or iso-osmolar contrast media • All patients regardless of their risk of developing CIN (as defined by risk factors such as age, cardiovascular and other comorbidity, creatinine level, etc.) • Patients using contrast media for any type of imaging study
Interventions	• IV volume expansion with saline • IV volume expansion with sodium bicarbonate • IV volume expansion with saline and sodium bicarbonate • IV or oral N-acetylcysteine, high-dose • IV fluids without pharmacologic agents • IV fluids with pharmacologic agents* • Oral fluids • Oral statins • IV dopamine • IV fluids matched to urine output • Discontinuation of metformin because of concern about inducing lactic acidosis • Discontinuation of medications that could have adverse effects on kidney function (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs) • Renal replacement therapy (e.g., hemodialysis or hemofiltration)
Comparators (see Table 2)	• Usual care vs. any of the interventions listed above • Volume expansion with saline vs. volume expansion with sodium bicarbonate • Volume expansion with saline vs. volume expansion with saline and sodium bicarbonate • Volume expansion with sodium bicarbonate vs. volume expansion with saline and sodium bicarbonate • High-dose vs. low-dose N-acetylcysteine • Timing and duration of above
Outcomes	• Short-term (≤7 days): a) Harms of prevention interventions – Imaging delay – Need for additional imaging – Fluid overload or heart failure b) Renal function measures – CIN as defined by change in serum creatinine or glomerular filtration rate c) Renal disease-specific outcomes – Need for renal replacement therapy (dialysis or hemofiltration) d) Other clinical outcomes – Mortality (in-hospital or within 7 days) – Cardiac outcomes e) Prolonged hospital stay • Long-term (>7 days): a) Renal function measures – Development of chronic kidney disease, including end stage renal disease – Rate of conversion to chronic kidney disease at 3 and 6 months – Chronic change in kidney function b) Renal disease-specific outcomes – Need for renal replacement therapy (dialysis, hemofiltration, or kidney transplant) c) Other clinical outcomes – Cardiac outcomes – Mortality in-hospital or at 3 or 6 months
Timing	• For short-term outcomes, any followup during hospitalization or within 7 days of procedure • For long-term outcomes, followup for more than 7 days • For observational studies, followup for at least 2 years.
Setting	• Inpatient and outpatient

CIN=contrast-induced nephropathy; IV=intravenous

* Pharmacological agents include: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, ascorbic acid, calcium antagonists, theophylline, aminophylline, dopamine, fenoldopam mesylate, atrial natriuretic peptide, statins, mannitol, MENSA fluid, allopurinol, furosemide, trimetazidine, anisodamine, probucol, and pentoxifylline.

Table 2. Major interventions for preventing contrast-induced nephropathy and main comparisons of interest (number of studies/total number of study participants)*

	IV Saline	IV $NaHCO_3$	IV or Oral NAC, High-Dose	IV or Oral NAC, low or High-Dose, Plus IV $NaHCO_3$	Adenosine Antagonists	RRT-HD or HF	Statins	Statins + NAC	IV Dopamine	Ascorbic Acid	IV Fluids With Other Drugs†
IV saline	13/4492‡	28/6645	18/5347	7/1745	5/475	6/790	8/5024		3/337	6/1025	21/2978
IV $NaHCO_3$											4/773
IV or oral NAC, low-dose	33/6270										
IV or oral NAC, low or high-dose	67/13176	7/1686						5/1477		3/583	23/4847

ACE= angiotensin-converting enzyme; HD=hemodialysis; HF=hemofiltration; IV=IV; NAC=N-acetylcysteine; $NaHCO_3$=sodium bicarbonate; RRT=renal replacement therapy
*These are the comparisons that had sufficient evidence to merit inclusion in this systematic review.
† Pharmacological agents include: ACE inhibitors, angiotensin receptor blockers, calcium antagonists, theophylline, aminophylline, dopamine, fenoldopam mesylate, atrial natriuretic peptide, statins, mannitol, MENSA fluid, allopurinol, furosemide, trimetazidine, anisodamine, probucol, and pentoxifline.
‡ Includes studies that compared all hydration regimens (oral and IV).

Organization of This Report

The following results section reports on a number of comparisons. We report in detail on comparisons for which substantial evidence exists, starting with the comparisons that have received the most attention in the literature (N-acetylcysteine plus IV saline versus IV saline, IV sodium bicarbonate versus IV saline, N-acetylcysteine plus IV saline versus IV sodium bicarbonate, statins plus IV saline versus IV saline, adenosine antagonists plus IV saline versus IV saline, renal replacement therapy versus IV saline, and ascorbic acid plus IV saline versus IV saline). At the end of the results section, we refer to information about other "miscellaneous comparisons" for which the studies were too few or too small to draw conclusions. Details on those comparisons appear in Appendixes H and I.

Methods

Topic Refinement and Protocol Review

We developed the Key Question with the input of a key informant panel that included: experts in nephrology, radiology, cardiology, and primary care; patient advocates; representatives from the Food and Drug Administration; and oversight by our Task Order Officer from the Agency for Health Care Research and Quality. We also recruited a technical expert panel to provide input on the protocol for the comparative effectiveness review.

Literature Search Strategy

We searched the following databases for primary studies through July 8, 2015: MEDLINE®, EMBASE®, and the Cochrane Library (see Appendix B for a detailed search strategy). We did not add any date limits to the search and developed a search strategy for MEDLINE, accessed via PubMed®, based on medical subject headings (MeSH®) terms and text words of key articles that we identified a priori. The search was not limited by language. In addition, we looked for conference proceedings and other reports by searching the Scopus database. We reviewed the reference lists of relevant articles and related systematic reviews to identify original journal articles and other reports the database searches might have missed. Scientific Information Packages were requested from a number of manufacturers, but no information was provided. We also searched ClinicalTrials.gov to identify on-going studies. We searched for publicly available data held by the U.S. Food and Drug Administration, but it has not approved any interventions for the prevention of CIN.

We uploaded articles into DistillerSR (Evidence Partners, Ottawa, Ontario, Canada), a Web-based service for systematic review and data management. We used this database to track search results at the levels of title review, abstract review, article inclusion/exclusion, and data abstraction.

Study Selection

We followed the PICOTS framework (Table 1) in developing the criteria for including studies in the review, and included studies of patients of all ages with low, moderate, or high risk of developing CIN. We anticipated heterogeneity in the pre-procedure risk assessment and reported on the heterogeneity as it was defined by the studies, which had to assess serum creatinine or glomerular filtration rate prior to and after contrast media injection. We only included studies in which the intervention group received either IOCM or LOCM via IV or intra-arterial injection. Studies had to report on at least one of the outcomes listed in the PICOTS framework. We included RCTs of comparisons detailed in the PICOTS, but focused the review on comparisons for which two or more studies reported on the same comparison. When we found interventions for which the comparisons were too heterogeneous to support an overall conclusion, we included a summary of the studies in the main report and placed details in an appendix. We included observational studies where available for all comparisons of interest. We evaluated previous systematic reviews on this topic to determine the extent to which they addressed our specific Key Question.

Data Extraction

Due to the volume of literature, we first screened titles and then screened abstracts for relevance to the Key Question. The titles and abstracts were screened independently by two reviewers. Inclusion at the title screening level was liberal; if a single reviewer believed an article might contain relevant information, the article was moved to the abstract level for further screening. When reviewing abstracts followed by the full text of articles, both reviewers had to agree on inclusion or exclusion. Disagreements that could not be resolved by the two reviewers were resolved by a third expert member of the team (see Appendix C for screening forms). At random intervals during screening, quality checks by senior team members were performed to ensure that the eligibility criteria were applied consistently.

Quality (Risk of Bias) Assessment of Individual Studies

Two reviewers independently assessed each study's risk of bias using five items from the Cochrane Risk of Bias tool for randomized studies[22]:

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Are reports of the study free of suggestion of selective outcome reporting?

When assessing the risk of bias, we focused on the main outcome of interest, CIN, an outcome that is objectively measured by laboratory testing.

Data Synthesis

We reviewed primary studies, as defined by our inclusion criteria, and we performed de novo meta-analyses. The de novo meta-analyses included all studies that met our inclusion criteria. Prior to conducting meta-analyses, clinicians discussed differences in the study design and reporting to identify characteristics that would limit the clinical meaningfulness of pooled results, such as the variability in outcome definitions, type of contrast media used, and route of contrast media administration. Differences in these items either prevented the statistical pooling with meta-analysis or were used to stratify the meta-analysis estimates.

Pooled risks of large comparison groups (with 18 or more studies) were calculated using a random effects model using the method of DerSimonian and Laird.[24] Because the DerSimonian and Laird method often underestimates confidence interval (CI) when there is a small number of studies (less than 18), for comparisons with less than 18 studies, the pooled risks were calculated using the Knapp-Hartung small sample estimator approach. This method allows for small sample adjustments to the variance estimates and forms CIs based on the t distribution with k - 1 degrees of freedom.[25] Statistical heterogeneity was assessed using the I-squared statistic. When the I-squared value was greater than or equal to 50%, or the p-value was 0.2 or less, the clinicians were asked to re-evaluate the studies for clinical heterogeneity and decide if the meta-analysis should be reported despite statistical heterogeneity. After reviewing the available evidence on all of the comparisons of interventions for preventing CIN, we felt that the heterogeneity across comparisons and the differences between reference groups were too great to support a network meta-analysis.

In many of the studies, the intervention group or the comparison group received more than one intervention. Therefore, we stratified the analyses according to the comparisons that were made, taking into consideration whether the intervention group or comparison group received more than one intervention. For example, we performed separate analyses for the following comparisons: N-acetylcysteine with IV saline versus IV saline with or without placebo; N-acetylcysteine with IV saline versus IV sodium bicarbonate; and N-acetylcysteine with IV sodium bicarbonate versus other interventions. The most common co-intervention was administration of fluids. We specified what fluid type was given whenever that was part of the intervention. For the analyses of N-acetylcysteine, all of the studies included IV fluids as a co-intervention with N-acetylcysteine, so we could not do a network meta-analysis or meta-regression to assess the effect of the co-intervention.

We used Harbord's modified test for small study effects to determine whether there was asymmetry in effect estimates when plotted against the standard error of the estimates, which can occur when publication bias exists.

Minimally Important Difference

To assess the clinical importance of differences in the incidence of CIN, a binary outcome, we followed guidance for selecting a minimally important difference based on the overall observed event rate in the studies.[26] Taking into consideration the potential effect of CIN on a patient's overall health and well-being, the clinical experts on our team decided that a relative risk reduction of 25% would be clinically important, which is consistent with the guidance suggesting a relative risk reduction of 20% to 30% in determining optimal information size.

Strength of the Body of Evidence

The team graded the strength of evidence on comparisons of interest for the key outcomes. We used the grading scheme recommended in the Methods Guide, and considered all domains: study limitations, directness, consistency, precision, reporting bias, and magnitude of effect.[27] Study limitations were determined for each comparison group for CIN and other reported outcomes. Study limitations were determined using the following algorithm for a body of evidence: A body of evidence was assessed as having <u>high</u> study limitations if greater than 50 percent of the studies scored negative in one or more of the criteria. A body of evidence was assessed as having <u>low</u> study limitations if most (51% or greater) of the studies scored positive in all five domains. Bodies of evidence not meeting one of the above criteria were assessed as having <u>medium</u> study limitations. Following the guidance of the GRADE Working Group,[26] we rated evidence as precise if the total number of patients exceeded an optimum information size, and the 95% confidence interval (CI) excluded a risk ratio of 1.0. If the total number of patients exceeded the optimum information size, and the 95% confidence interval did not exclude the possibility of no difference (i.e., risk ratio of 1.0), we only rated the evidence as precise if the 95% confidence interval excluded the possibility of a clinically important benefit or harm (i.e., risk ratio less than 0.75 or greater than 1.25). For the main outcome of interest, CIN, we used an optimum information size of 2000 based on an expected 0.1 probability of CIN in the comparison group and a minimally important relative difference of 25%. For less frequent adverse outcomes, we used an optimum information size of 10,000 based on an expected 0.02 probability in the comparison group and a minimally important relative difference of 25%. We classified the strength of evidence pertaining to each comparison into four grades: high, moderate, low, and insufficient. The body of evidence was considered high grade if study limitations were low and there were no problems in any of the other domains, and subsequently downgraded for each domain in which a problem was identified. If only one study was available for a given comparison, we downgraded the evidence for having unknown consistency. If the magnitude of effect was very large, the strength of evidence could be upgraded.

Observational studies were considered in grading the strength of a body of evidence if the overall results of the observational studies were not similar to the RCTs applicable to the comparison.

Applicability

We considered elements of the PICOTS framework (Table 1) when evaluating the applicability of evidence to answer our Key Question as recommended in the Methods Guide.[27] This includes important population characteristics, treatment characteristics, and settings that may cause heterogeneity of treatment effects and limit applicability of the findings.

Results

Results of the Literature Search

The literature search identified 12,523 unique citations, and we ultimately found 163 RCTs and 23 observational studies that met the eligibility criteria (Figure 2 and Appendix D). None of the previous systematic reviews we found addressed the overall objectives of this review well enough to serve as the basis for an update instead of a comprehensive de novo review.

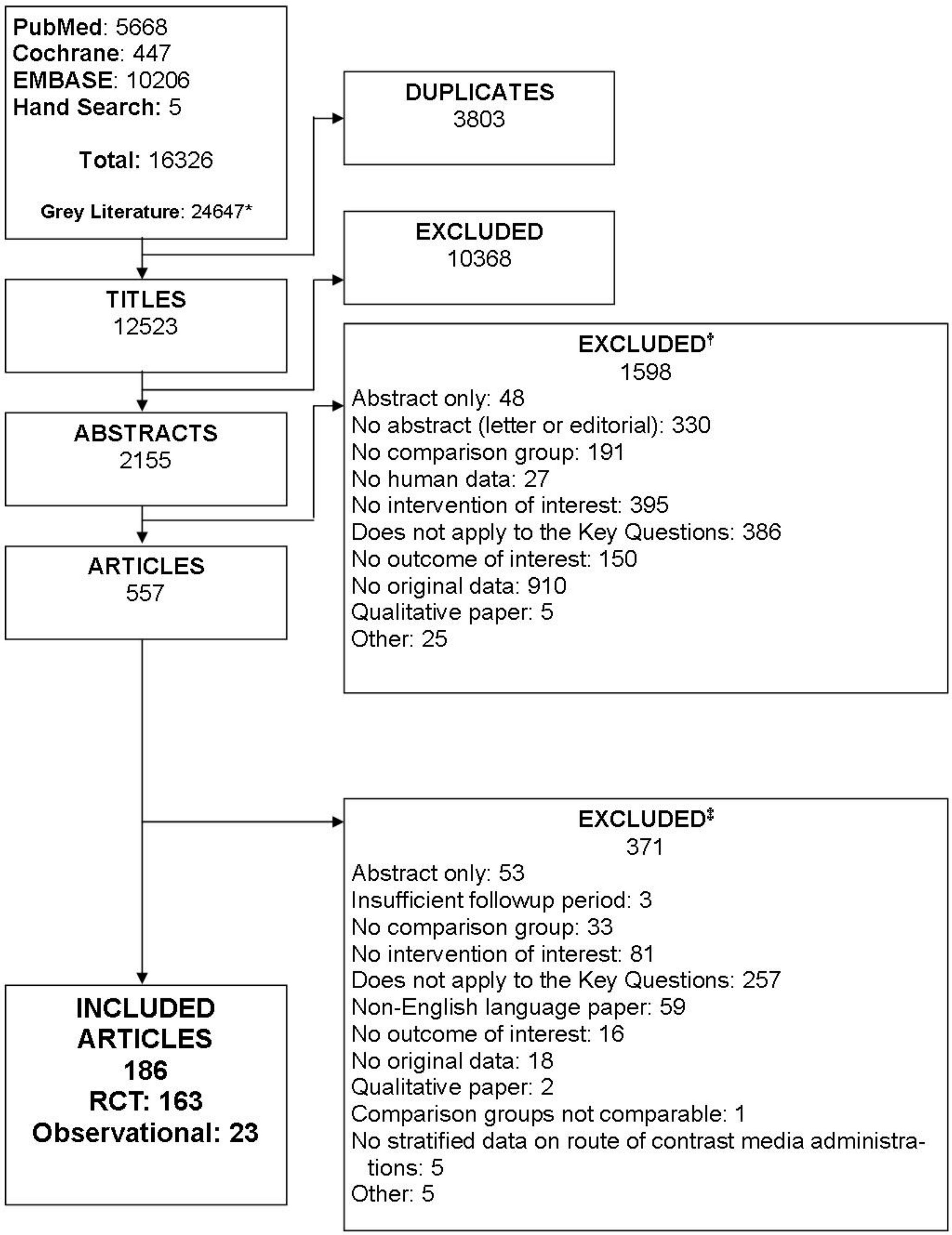
Key Question: In patients undergoing imaging studies requiring intravenous (IV) or intra-arterial contrast media, what is the comparative effectiveness of interventions to prevent contrast-induced nephropathy for the outcomes of incidence of contrast-induced nephropathy, chronic kidney disease, end stage renal disease, mortality, and other adverse events?

Key Points

- Low-dose N-acetylcysteine (1200 mg/day or less) had a small, borderline clinically important effect in reducing contrast-induced nephropathy (CIN) compared to IV saline, with low strength of evidence (pooled risk ratio 0.75; 95% CI: 0.63 to 0.89).
- High-dose N-acetylcysteine (more than 1200 mg/ day) had a small clinically unimportant effect in reducing CIN compared to IV saline, with low strength of evidence (pooled risk ratio 0.78; 95% CI: 0.59 to 1.03).
- A clinically important and statistically significant reduction in CIN was seen when N-acetylcysteine was compared with IV saline in patients receiving LOCM, with moderate strength of evidence (pooled risk ratio 0.69; 95% CI: 0.58 to 0.84), but not in patients receiving IOCM, with low strength of evidence (pooled risk ratio 1.12; 95% CI: 0.74 to 1.69). The risk ratio estimates did not differ between IV and intra-arterial routes of administration of contrast media.
- The strength of evidence was low that IV sodium bicarbonate with IV saline did not differ from IV saline in the risk of CIN (pooled risk ratio 0.93; 95% CI: 0.68 to 1.27). However, IV sodium bicarbonate was more effective than IV saline in preventing CIN with a clinically important benefit when given for studies with LOCM only (pooled risk ratio: 0.65; 95% CI: 0.33 to 1.25) with low strength of evidence, but not when given for studies with IOCM (pooled risk ratio 1.02; 95% CI: 0.70 to 1.48), with low strength of evidence.
- Statins plus IV saline had a clinically important effect in reducing CIN compared to IV saline, but the difference was not statistically significant, with low strength of evidence (pooled risk ratio 0.68; 95% CI: 0.39 to 1.20). Statins plus N-acetylcysteine had a clinically important effect in reducing CIN compared to N-acetylcysteine alone, with low strength of evidence (pooled risk ratio 0.52; 95% CI: 0.29 to 0.93).
- Hemodialysis did not reduce the risk of CIN and may be harmful compared to IV saline (pooled risk ratio 1.50; 95% CI: 0.56 to 4.04), with low strength of evidence.
- When compared to IV saline, ascorbic acid plus IV saline had a small clinically important but statistically insignificant effect on CIN (pooled risk ratio 0.72; 95% CI: 0.48 to 1.01), with low strength of evidence.

- The strength of evidence was insufficient to determine the effect of other interventions on the incidence of CIN.

Figure 2. Results of the literature search



RCT = randomized controlled trial
*Grey literature was not factored into the total number of studies for title screening.
†Sum of excluded abstracts exceeds 1,598 because reviewers were not required to agree on reasons for exclusion.
‡Sum of excluded articles exceeds 371 because reviewers were not required to agree on reasons for exclusion.

N-Acetylcysteine Plus IV Saline Versus IV Saline With or Without Placebo

Although the pathophysiology of CIN is not completely understood, it is thought that renal medullary ischemia and direct toxicity to renal tubules by oxygen free radicals may contribute. N-acetylcysteine is a direct scavenger of free radicals and improves blood flow through nitric oxide-mediated pathways, which results in vasodilation. As a result, both the antioxidant and vasodilatory properties of N-acetylcysteine are thought to provide protection against CIN.

Although early studies showed benefits of N-acetylcysteine in patients receiving HOCM or LOCM, subsequent studies and meta-analyses offer mixed results concerning the efficacy of N-acetylcysteine for prevention of CIN. It is possible that the effectiveness of N-acetylcysteine depends on the administered dose and route of administration of N-acetylcysteine, the osmolality of contrast media and its route of administration, and study population characteristics.

Study Characteristics

Seventy eight studies (67 RCTs and 11 observational studies) were identified that compared N-acetylcysteine with IV saline. Of these, 74 reported on CIN directly, and three reported on serum creatinine or glomerular filtration rate without reporting the incidence of CIN. Of the studies reporting on CIN directly, we found 54 RCTs that compared N-acetylcysteine plus IV saline with IV saline with or without placebo, published between 2002 and 2014, which we included in a meta-analysis. The number of patients in each trial ranged from 40 to 3382, and the study populations were very heterogeneous across the studies. Study patients had renal dysfunction at baseline (defined as baseline serum creatinine greater than 1.2 mg/dl) in 35 studies.[28-62] The mean age of patients included in the studies was 55 to 79 years, the mean percentage of patients with diabetes was 39 percent (range 0% to 100%), and the mean percentage of females was 32 percent (range 12% to 59%).

Across all of the studies included in the meta-analysis, 4749 patients received IV saline with or without placebo, and 4775 received N-acetylcysteine. The route and dose of N-acetylcysteine varied between studies. Forty studies administered N-acetylcysteine orally,[28-33,36-43,45-47,49,50,52-56,59-74] 13 administered it intravenouly,[34,35,44,48,51,57,58,75-80] and one used a combination of IV and oral N-acetylcysteine.[81] Thirty-four studies,[28-36,39,41-47,49-52,56,59-63,65,67,68,70,71,74,78] used a low-dose of N-acetylcysteine (1200 mg/day or less), and 18 studies used a higher dose (greater than 1200 mg/day)[37,38,40,48,53-55,57,58,64,66,69,75-77,79-81] One study had one arm with low-dose N-acetylcysteine, a second arm with high-dose N-acetylcysteine, and a control arm that received a placebo in IV saline.[81]

Contrast media was administered intravenously in seven studies,[36,44,49,57,62,68,79] not described in one study,[46] and intra-arterially in the remaining studies. Seven studies used IOCM,[32,36,39,69,70,76] six used either IOCM or LOCM;[28,29,60,67,69,79] one used IOCM, LOCM, or HOCM;[69] one did not report the contrast media type,[73] and the remainder used LOCM.

Variation existed in the protocols for giving fluids, with studies using 0.45 percent saline; normal saline; 5 percent dextrose in normal saline, or alone; or Ringer's lactate solutions. The studies administered varying volumes and used three definitions of CIN: 0.5 mg/dl absolute increase, 25 percent increase in serum creatinine, and a combination of both. All of the studies except three measured the change in serum creatinine between 48 and72 hours. One measured the change in serum creatinine at 24 hours,[48] one measured it between 48 and 96 hours,[69] and one study measured the change five days after contrast media administration[71] (Appendix E, Evidence Table E-4).

Contrast-Induced Nephropathy

The 54 RCTs comparing N-acetylcysteine plus IV saline to IV saline with or without placebo in the reduction of CIN showed a range of results included in the meta-analyses: seven reported a clinically important reduction in the risk of CIN that was statistically significant, 20 reported a clinically important reduction in the risk of CIN that was not statistically significant, 10 did not show a clinically important reduction in the risk of CIN, 12 did not show a clinically important increased risk of CIN, two showed a clinically important increased risk of CIN that was not statistically significant, and three showed a clinically and statistically significant increased risk of CIN.

The pooled risk ratio of CIN, using the DerSimonian and Laird random effects model, was 0.78 (95% CI: 0.59 to 1.03) for high-dose N-acetylcysteine (greater than 1200 mg/day), indicating that, on average, the effect is at a level consistent with a clinically unimportant reduction in CIN (Figure 3). There was moderate statistical heterogeneity across studies with an I-squared of 38%. The pooled risk ratio for CIN from the studies using intra-arterially administered contrast media and high-dose N-acetylcysteine was 0.78 (95% CI: 0.55 to 1.12) (high-dose N-acetylcysteine with intra-arterial contrast media administration pooled risk ratio was run with Knapp-Hartung method). Two studies used IV contrast media and high-dose N-acetylcysteine, and their results were too imprecise to draw conclusions (pooled risk ratio 0.55; 95% CI: 0.12 to 2.62). Using Harbord's modified test for small study effects, we did not find evidence of asymmetry in results by study precision (bias coefficient of -0.61, standard error of 0.66, p=0.37). The strength of evidence was low that high-dose N-acetylcysteine with IV saline had a small clinically unimportant effect in preventing CIN compared with IV saline with or without placebo. (Table 3; see Appendixes F and G for study limitations).

The pooled risk ratio for CIN using a random effects model for low-dose N-acetylcysteine (1200 mg/day or less) was 0.75 (95% CI: 0.63 to 0.89), indicating that, on average, the small effect is consistent with a borderline clinically important reduction in CIN (Figure 4). The statistical heterogeneity of the studies was low, with an I-squared of 0%. The pooled risk ratio using the Knapp-Hartung method for the studies using IV contrast media and low-dose N-acetylcysteine was 0.62, but in this small subset of five studies, the confidence interval was so wide that we cannot rule out a clinically important increased risk (95% CI: 0.18 to 2.10). For studies using intra-arterially administered contrast media and low-dose N-acetylcysteine, the pooled risk ratio was 0.77 (95% CI: 0.66 to 0.91) indicating that, on average, the benefit is at a level consistent with a clinically unimportant reduction in CIN. Using Harbord's modified test for small study effects, we did not find evidence of asymmetry in results by study precision (bias coefficient of -0.70, standard error of 0.44, p=0.123). Overall, the strength of evidence was low that low-dose N-acetylcysteine with IV saline had a small clinically unimportant effect in preventing CIN compared with IV saline with or without a placebo (Table 3; see Appendixes F and G for study limitations).

We performed stratification analyses to investigate the influence of contrast media osmolality on the effect of N-acetylcysteine. The pooled risk ratio of CIN, using a random effects model, for studies using LOCM was 0.69 (95% CI: 0.58 to 0.84), indicating that, on average, the difference is consistent with a clinically important reduction in CIN with N-acetylcysteine in patients receiving LOCM, but the confidence interval does not rule out a clinically unimportant difference (Figure 5).The statistical heterogeneity across studies was low, with an I-squared of 19 percent. The strength of the evidence was moderate that in patients receiving LOCM, N-acetylcysteine with IV saline had a clinically important reduction in CIN. The pooled risk ratio for CIN from studies of N-acetylcysteine using IOCM was 1.12 (95% CI: 0.74 to 1.69). The confidence interval was wide enough for N-acetylcysteine when IOCM was used to suggest possible harm without any indication of a clinically important benefit (Figure 6). The strength of the evidence was low that in patients receiving IOCM, N-acetylcysteine with IV saline did not have a clinically important decrease in CIN. The estimates of effect are remarkably stable across different types of studies with a 20 to 30 percent reduction, which is near the edge of what we defined to be a minimally important difference. The variation is mainly in the CIs, which is likely due to variation in the number of people in the different studies.

We also performed stratification analyses to investigate the influence of the route of N-acetylcysteine administration. The pooled risk ratio for CIN, using a random effects model, for patients who received oral N-acetylcysteine was 0.77 (95% CI: 0.65 to 0.92), indicating that, on average, the difference is not clinically important. The pooled risk ratio for CIN for patients who received IV N-acetylcysteine (run with the Knapp-Hartung method) was 0.90 (95% CI: 0.72 to 1.12), indicating that the difference is not clinically important (Figure 7).

Our sensitivity analysis, which removed one study at a time, did not show any significant impact on the estimated effect of N-acetylcysteine. When we examined the variation of risk ratio estimates according to baseline characteristics of the study population, we did not observe any meaningful difference by age, sex, baseline renal function, or the presence or absence of diabetes mellitus. There was no trend in the effect size by year of the study publication (Figure 7). When we examined how the results of studies of N-acetylcysteine varied in forest plots organized by the number of study limitations, we did not see any pattern indicative of a trend by study quality.

Thirteen of the 67 RCTs reporting on CIN were not included in the meta-analyses for a variety of reasons, including missing data, dosage differences, and inclusion criteria differences (see Appendix E, Evidence Table E-5).[67,82-90] In addition to the studies that reported on the incidence of CIN, three studies reported on changes in serum creatinine (Appendix E, Evidence Table E-6) and/or glomerular filtration rate (Appendix E, Evidence Table E-7) without reporting the incidence of CIN.[91-93] In those nine studies, the mean change in serum creatinine or glomerular filtration rate did not differ enough between groups to meet the definition of CIN.

Eleven observational studies were included in the studies we reviewed.[94-104]The results of the observational studies were similar to those reported in the RCTs.

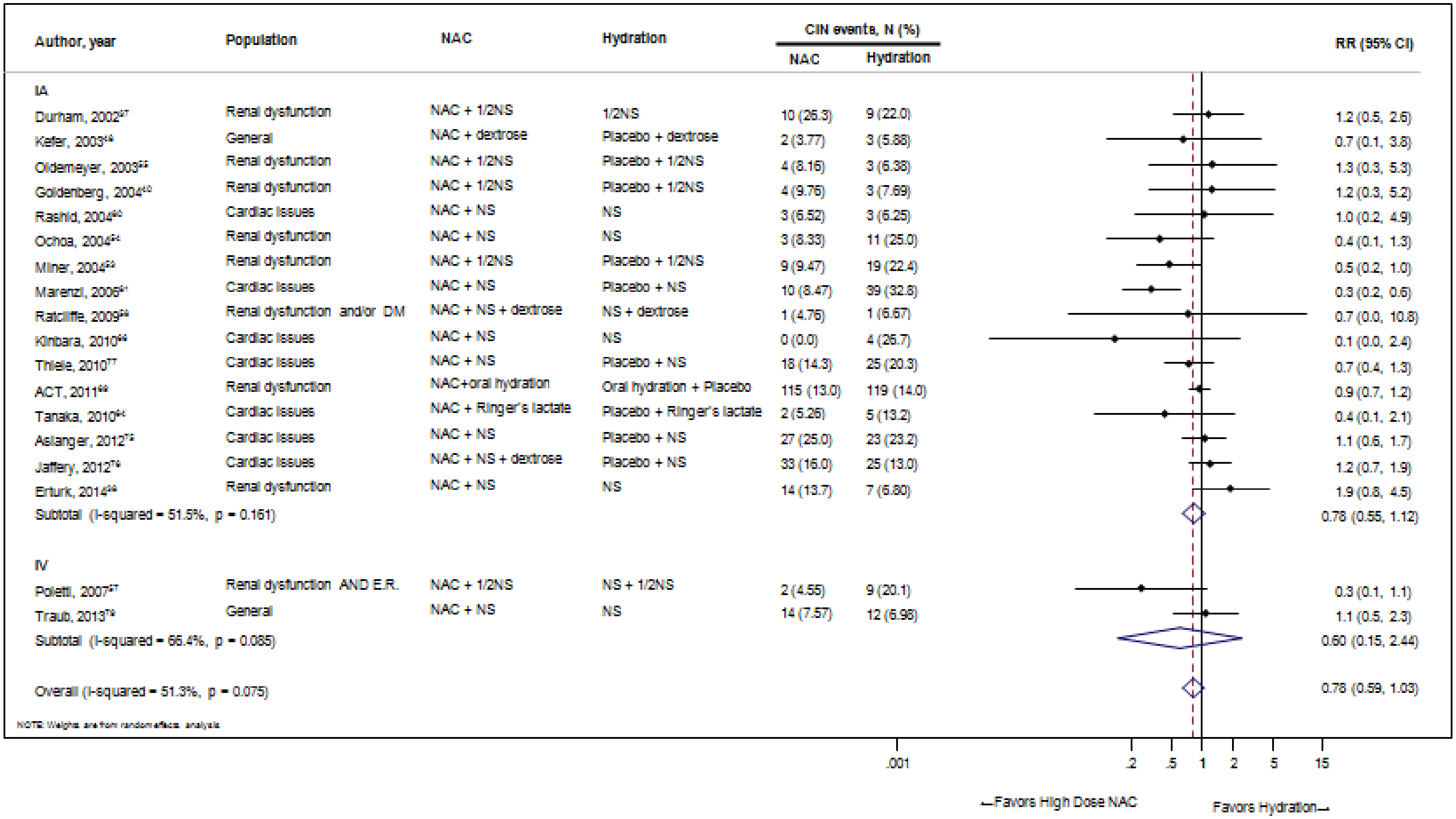
Other Outcomes

Of the 77 studies investigating development of CIN when comparing N-acetylcysteine plus IV saline with a placebo with or without IV saline, 35 also included data on secondary outcomes. Twenty eight reported patients' needs for renal replacement therapy,[28,30,33,35,37-39,41,44-46,51,53,55,56,59,61,69-71,80-85,87,89] seven reported cardiac events,[31,38,40,53,70,71,82] 14 reported mortality,[30,35,38,39,41,44,53,59,69,76-78,81,83] and nine reported length of hospitalization (Appendix E, Evidence Table E-8).[35,47,56,64, 71,76-78,83]

Of the 20 studies that examined the need for renal replacement therapy, only seven reported p-values and one reported a statistically insignificant, and clinically non-significant difference between groups (risk ratio: 0.87; 95% CI: 0.17-4.35).[69] The remaining studies reporting on the need for renal replacement therapy did not report statistics. One study, Marenzi et al.,2006,[81] reported a statistically significant and clinically important difference in mortality between the placebo arm and the N-acetylcysteine arms, with more in-hospital deaths in the placebo arm (placebo: 13/119 (11%); standard dose N-acetylcysteine: 5/115 (4%); high-dose N-acetylcysteine: 3/118 (3%), p=0.007).[81] Two studies reported significant findings for length of hospitalization. Hsu et al., 2007[71] showed a statistically significant and clinically important reduction in length of hospitalization in the N-acetylcysteine arm (placebo: mean 8.1 days, standard deviation (SD) 4.1); low-dose N-acetylcysteine arm (mean 5.2 days, SD 1.5); p=0.04)).[71] Kay et al., 2003[47] also showed a statistically significant reduction in length of hospitalization in the N-acetylcysteine arm, but the difference was not clinically important (placebo: mean 3.9 days, SD 2.0); low-dose N-acetylcysteine: mean 3.4 days, SD 0.9: p=0.02).[47] No clinically important or statistically significant differences were reported for cardiac events.

Overall, the strength of evidence was low that N-acetylcysteine plus IV saline did not differ from IV saline without N-acetylcysteine in the need for renal replacement therapy, cardiac events, or the length of hospitalization. (Table 3; Appendix E, Evidence Table E-8; see Appendix G for study limitations). Most of the studies addressing these outcomes had at least one important study limitation (frequently lacking documentation of allocation concealment or blinding of participants and personnel). The results generally were consistent in the direction of impact of N-acetylcysteine. However, the effect estimates were imprecise. The studies addressing mortality had insufficient strength of evidence to support a conclusion because they had important study limitations, with inconsistent and imprecise effect estimates.

Figure 3. Meta-analysis of high-dose* N-acetylcysteine plus IV saline versus IV saline with or without placebo for the prevention of contrast-induced nephropathy



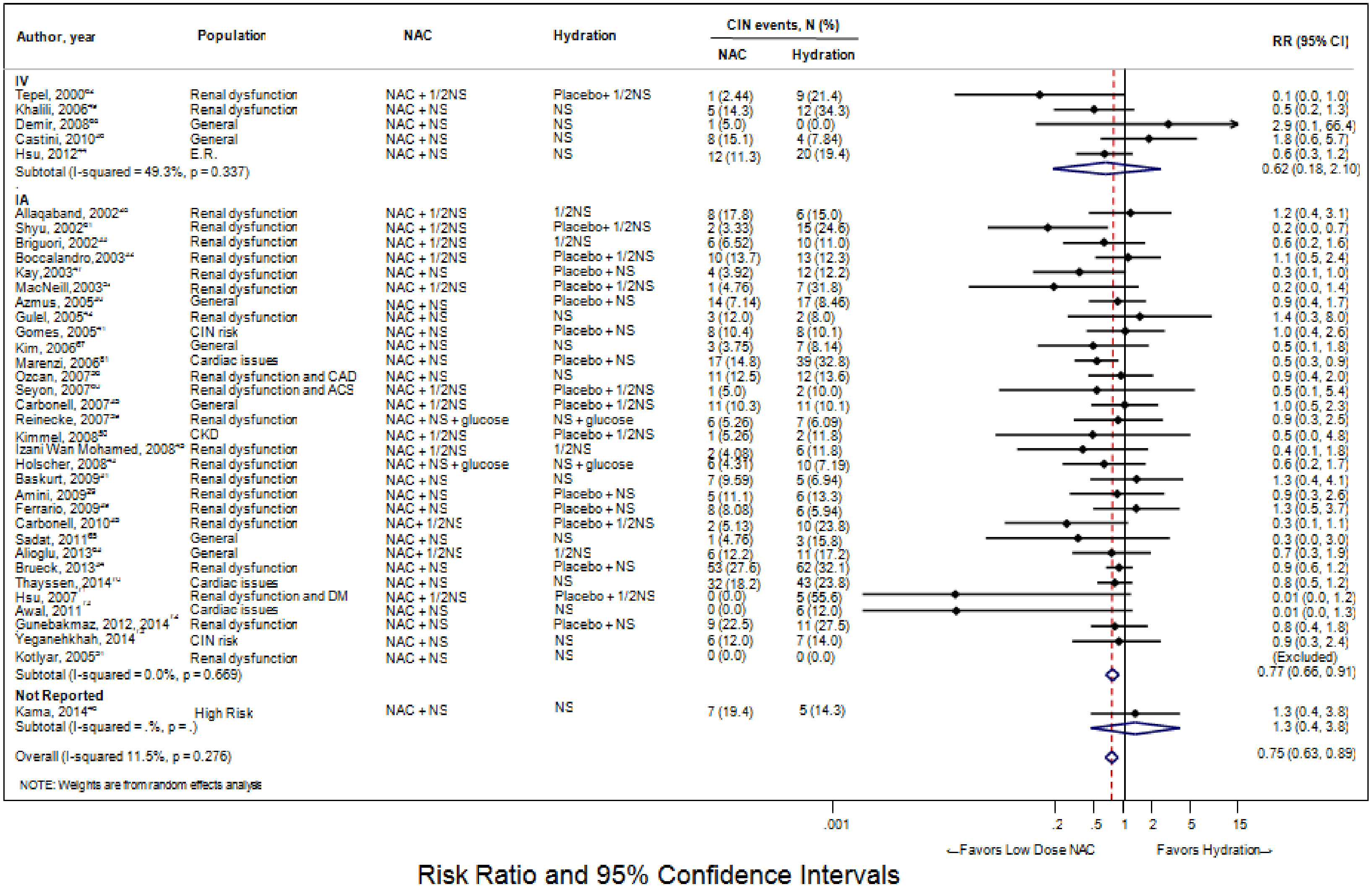
Author, year	Population	NAC	Hydration	CIN events, N (%) NAC	CIN events, N (%) Hydration	RR (95% CI)
IA						
Durham, 2002[47]	Renal dysfunction	NAC + 1/2NS	1/2NS	10 (26.3)	9 (22.0)	1.2 (0.5, 2.6)
Kefer, 2003[49]	General	NAC + dextrose	Placebo + dextrose	2 (3.77)	3 (5.88)	0.7 (0.1, 3.8)
Oldemeyer, 2003[55]	Renal dysfunction	NAC + 1/2NS	Placebo + 1/2NS	4 (8.16)	3 (6.38)	1.3 (0.3, 5.3)
Goldenberg, 2004[40]	Renal dysfunction	NAC + 1/2NS	Placebo + 1/2NS	4 (9.76)	3 (7.69)	1.2 (0.3, 5.2)
Rashid, 2004[60]	Cardiac issues	NAC + NS	NS	3 (6.52)	3 (6.25)	1.0 (0.2, 4.9)
Ochoa, 2004[54]	Renal dysfunction	NAC + NS	NS	3 (8.33)	11 (25.0)	0.4 (0.1, 1.3)
Miner, 2004[53]	Renal dysfunction	NAC + 1/2NS	Placebo + 1/2NS	9 (9.47)	19 (22.4)	0.5 (0.2, 1.0)
Marenzi, 2006[51]	Cardiac issues	NAC + NS	Placebo + NS	10 (8.47)	39 (32.8)	0.3 (0.2, 0.6)
Ratcliffe, 2009[58]	Renal dysfunction and/or DM	NAC + NS + dextrose	NS + dextrose	1 (4.76)	1 (6.67)	0.7 (0.0, 10.8)
Kinbara, 2010[66]	Cardiac issues	NAC + NS	NS	0 (0.0)	4 (26.7)	0.1 (0.0, 2.4)
Thiele, 2010[77]	Cardiac issues	NAC + NS	Placebo + NS	18 (14.3)	25 (20.3)	0.7 (0.4, 1.3)
ACT, 2011[69]	Renal dysfunction	NAC+oral hydration	Oral hydration + Placebo	115 (13.0)	119 (14.0)	0.9 (0.7, 1.2)
Tanaka, 2010[64]	Cardiac issues	NAC + Ringer's lactate	Placebo + Ringer's lactate	2 (5.26)	5 (13.2)	0.4 (0.1, 2.1)
Aslanger, 2012[73]	Cardiac issues	NAC + NS	Placebo + NS	27 (25.0)	23 (23.2)	1.1 (0.6, 1.7)
Jaffery, 2012[76]	Cardiac issues	NAC + NS + dextrose	Placebo + NS	33 (16.0)	25 (13.0)	1.2 (0.7, 1.9)
Erturk, 2014[65]	Renal dysfunction	NAC + NS	NS	14 (13.7)	7 (6.80)	1.9 (0.8, 4.5)
Subtotal (I-squared = 51.5%, p = 0.161)						0.78 (0.55, 1.12)
IV						
Poletti, 2007[57]	Renal dysfunction AND E.R.	NAC + 1/2NS	NS + 1/2NS	2 (4.55)	9 (20.1)	0.3 (0.1, 1.1)
Traub, 2013[79]	General	NAC + NS	NS	14 (7.57)	12 (6.98)	1.1 (0.5, 2.3)
Subtotal (I-squared = 66.4%, p = 0.085)						0.60 (0.15, 2.44)
Overall (I-squared = 51.3%, p = 0.075)						0.78 (0.59, 1.03)

NOTE: Weights are from random effects analysis

%=percent; 1/2NS=0.45% saline; CI=confidence interval; CIN=contrast induced nephropathy; DM=diabetes mellitus; ER=emergency room; IA=intra-arterial; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NS=normal saline (0.9%); p=p-value; RR=risk ratio

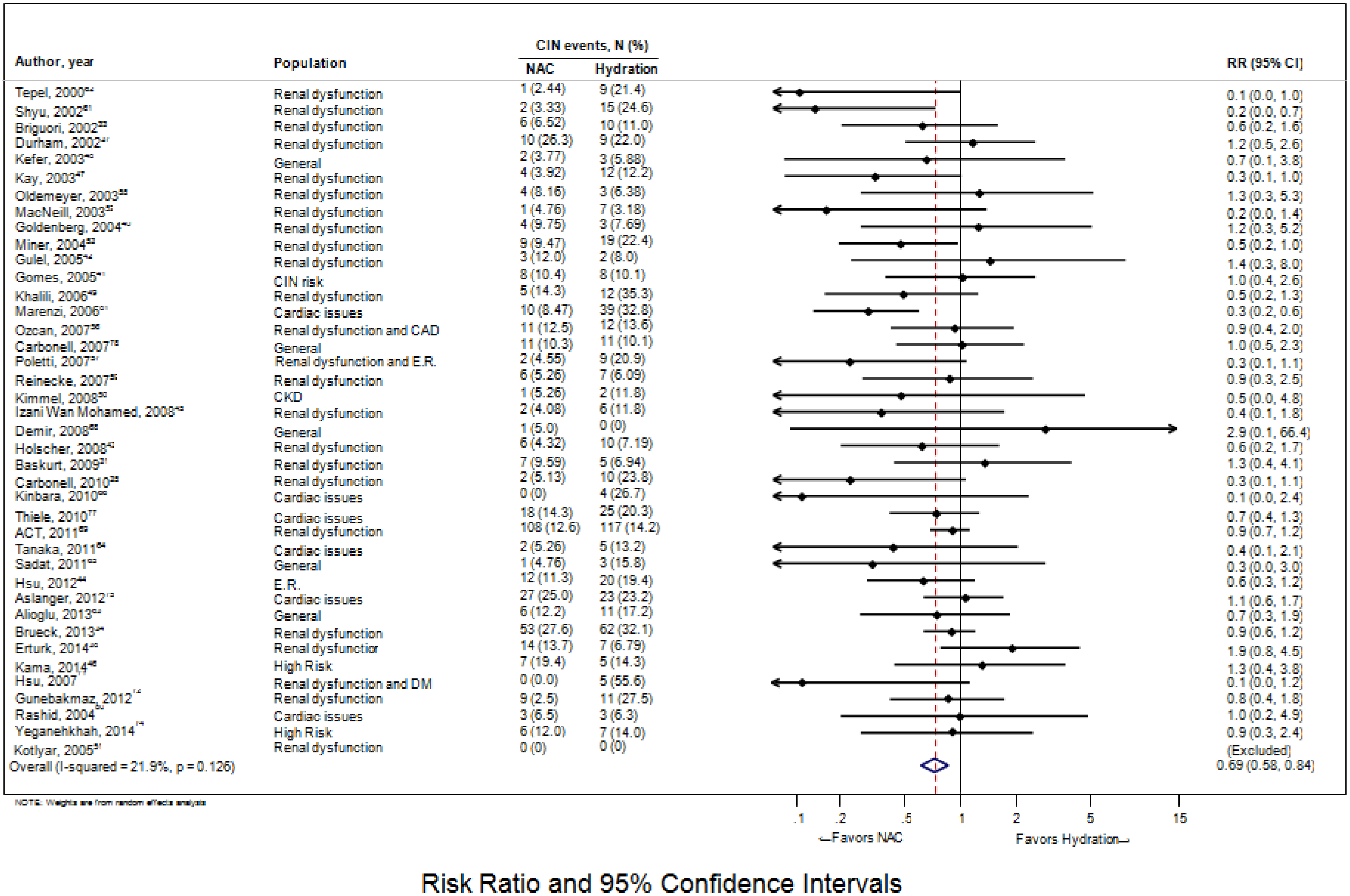
*High-dose N-acetylcysteine refers to studies that administered more than 1200mg N-acetylcysteine daily to participants.

Figure 4. Meta-analysis of low-dose* N-acetylcysteine plus IV saline versus IV saline with or without placebo for the prevention of contrast-induced nephropathy



%=percent; 1/2NS=0.45% saline; ACS=acute coronary syndrome; CAD=coronary artery disease; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; ER=emergency room; IA=intra-arterial; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NS=normal saline (0.9%); p=p-value; RR=risk ratio
*Low-dose N-acetylcysteine refers to studies that administered 1200mg or less of N-acetylcysteine daily to participants.

Figure 5. Meta-analysis of N-acetylcysteine plus IV saline versus IV saline with or without placebo for the prevention of contrast-induced nephropathy when low-osmolar contrast is used

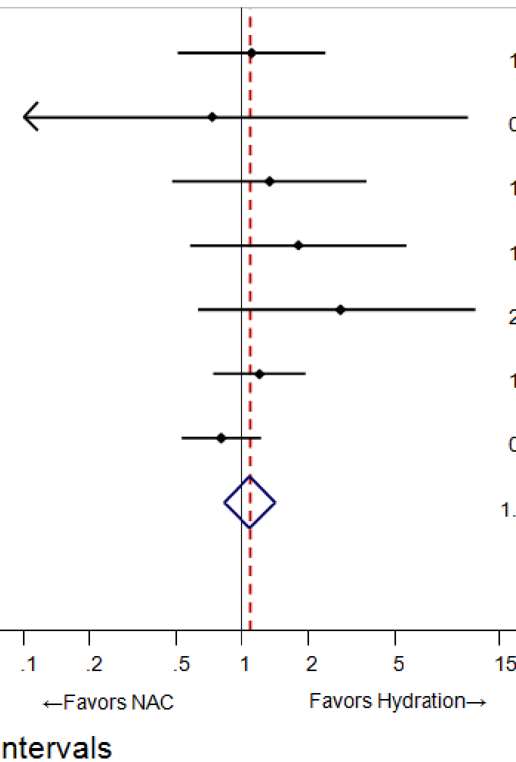


%=percent; CAD=coronary artery disease; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; ER=emergency room; N=sample size; NAC=N-acetylcysteine; p=p-value; RR=risk ratio

Figure 6. Meta-analysis of N-acetylcysteine plus IV saline versus IV saline with or without placebo for the prevention of contrast-induced nephropathy when iso-osmolar contrast is used

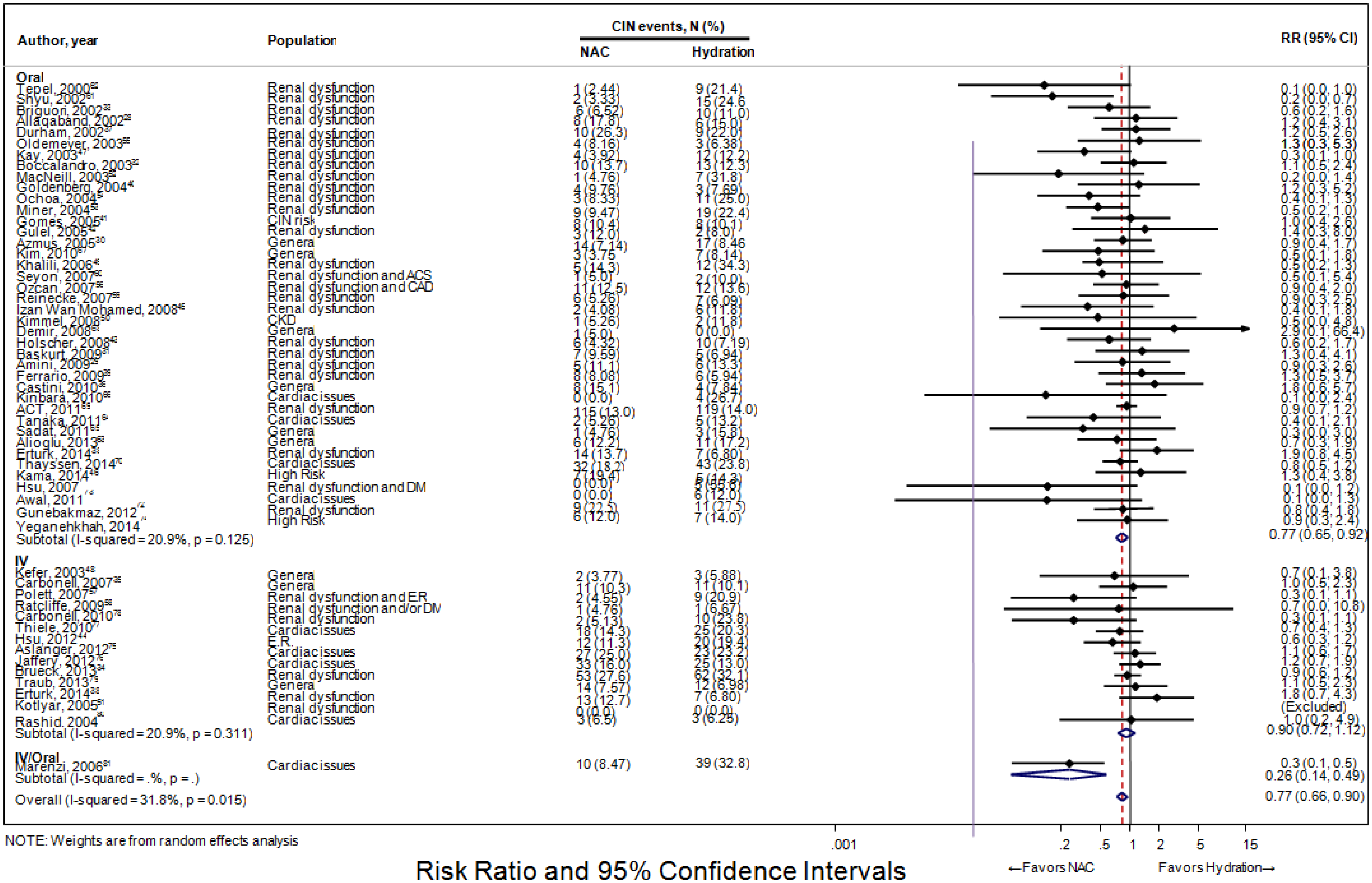
Author, year	Population	NAC	NAC Dose	Hydration	CIN events, N (%) NAC	CIN events, N (%) Hydration	RR (95% CI)
Boccalandro, 2003[32]	Renal dysfunction	NAC + 1/2NS	Low	Placebo + 1/2NS	10 (13.7)	13 (12.26)	1.1 (0.5, 2.4)
Ratcliffe, 2009[58]	Renal dysfunction and/or DM	NAC + NS + dextrose	High	NS + dextrose	1 (4.76)	1 (6.66)	0.7 (0.0, 10.8)
Ferrario, 2009[35]	Renal dysfunction	NAC + NS	Low	Placebo + NS	8 (8.08)	6 (5.94)	1.3 (0.5, 3.7)
Castini, 2010[36]	General	NAC + NS	Low	NS	8 (15.1)	4 (7.84)	1.8 (0.6, 5.7)
ACT, 2011[69]	Renal	NAC+oral hydration	High	Oral Hydration + Placebo	7 (20.6)	2 (6.45)	2.8 (0.6, 12.7)
Jaffery, 2012[76]	Cardiac issues	NAC + NS	High	Placebo + NS	33 (16.02)	25 (13.02)	1.2 (0.7, 1.9)
Thayssen, 2014[70]	Cardiac issues	NAC + NS	Low	NS	32 (18.18)	43 (23.76)	0.8 (0.5, 1.2)
Overall (I-squared = 4.66%, p = 0.541)							1.12 (0.74, 1.69)

NOTE: Weights are from random effects analysis



%=percent; CAD=coronary artery disease; CI=confidence interval; CIN=contrast induced nephropathy; DM=diabetes mellitus; N=sample size; NAC=N-acetylcysteine; p=p-value; RR=risk ratio; NS=normal saline (0.9%); 1/2NS=0.45% saline

Figure 7. Meta-analysis of oral and IV route of N-acetylcysteine plus IV saline versus IV saline with or without placebo for the prevention of contrast-induced nephropathy



%=percent; ACS=acute coronary syndrome; CAD=coronary artery disease; CI=confidence interval; CIN=contrast induced nephropathy; DM=diabetes mellitus; ER=emergency room; IV/Oral=intravenous or oral NAC administration; IV=intravenous; N=sample size; NAC=N-acetylcysteine; p=p-value; RR=risk ratio

Table 3. Summary of the strength of evidence: N-acetylcysteine plus IV saline versus IV saline with or without placebo

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Outcomes
Development of CIN (high-dose NAC)	RCT: 18 (4336)	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that high-dose NAC with IV saline has a small clinically unimportant benefit in preventing CIN compared with IV saline without NAC
Development of CIN (low-dose NAC)	RCT: 36 (5217)	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that low-dose NAC with IV saline has a small clinically unimportant benefit in preventing CIN compared with IV saline without NAC
Development of CIN (in patients receiving LOCM)	RCT: 40 (6665)	Medium	Direct	Consistent	Precise	Moderate	Moderate strength of evidence that NAC with IV saline has a clinically important benefit in preventing CIN compared with IV saline without NAC in patients receiving LOCM
Development of CIN (in patients receiving IOCM)	RCT: 7 (1339)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not have a clinically important decrease in CIN compared with IV saline without NAC in patients receiving IOCM
Need for RRT	RCT: 20 (4881)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in preventing need for RRT
Cardiac events	RCT: 7 (1207)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in preventing cardiac events
Mortality	RCT: 14 (4592)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence regarding effect of NAC with IV saline on preventing mortality compared with IV saline alone
Hospitalization, length of stay	RCT: 9 (1461)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC with IV saline does not differ from IV saline alone in reducing length of hospitalization

CIN=contrast-induced nephropathy; IV = IV; N=sample size; NAC=N-acetylcysteine; RCT=randomized controlled trial; RRT=renal replacement therapy

IV Sodium Bicarbonate Versus IV Saline

A major underlying hypothesis for using IV sodium bicarbonate to prevent CIN is that the alkalinization of tubular fluid diminishes the production of free oxygen radicals, which may play a role in the etiology of CIN.[105] Some studies demonstrated a benefit for IV sodium bicarbonate were inconclusive.[106,107] Prior meta-analyses showed a mixed effect for IV sodium bicarbonate.[108]

Study Characteristics

Thirty articles were identified that compared IV sodium bicarbonate with IV saline (28 RCTs and 2 observational studies). Nineteen RCTs[36,46,56,58,70,74,109-121] published between 2004 and 2014 were included in the meta-analysis; the two observational studies were not included in the meta-analysis.[122,123]

In these studies, CIN was defined three ways (Appendix E, Evidence Tables E-1, E-3, E-10): five defined it as a 25 percent or greater increase in serum creatinine, one defined it as a 0.5 mg/dl or greater increase in serum creatinine, and seven defined it as either a 25 percent or greater increase or a 0.5 mg/dl or greater increase in serum creatinine.

A total of 1748 patients were included in the control arms, and 1750 patients were included in the sodium bicarbonate arms. The mean age of patients was 65.8 years (range 59 to 77 years). The mean percentage of diabetes patients was 44 percent (range 6–100%) and the mean percentage of female patients was 29.4 percent (range 5–48%). Contrast media administration was intra-arterial in fourteen studies,[36,56,58,70,74,109,111-113,115-117,119-121] IV in two studies, [110,114] both IV and intra-arterial in three studies.[46,110,118] Two studies used IOCM,[36,115] and the other studies used LOCM (Appendix E, Evidence Tables E-2, E-10).

Contrast-Induced Nephropathy

Six studies concluded that IV sodium bicarbonate administration reduced the incidence of CIN when compared with IV saline, while thirteen reported no difference in the incidence of CIN between the IV sodium bicarbonate and IV saline intervention arms. The meta-analysis indicated that administration of IV sodium bicarbonate did not differ from IV saline in the risk of CIN (pooled risk ratio 0.93; 95% CI: 0.68 to 1.27), with a point estimate indicating a difference that was not clinically important, and a wide confidence interval that did not rule out the possibility of an important reduction or important increase in CIN (see Figure 8). However, as shown in Figure 8, IV sodium bicarbonate with IV saline was more effective than IV saline in preventing CIN, with a clinically important benefit, in a subset of 11 studies using LOCM (pooled risk ratio 0.65; 95% CI: 0.33 to 1.25), but not in the subset of 7 studies using IOCM (pooled risk ratio 1.02; 95% CI: 0.70 to 1.48). The strength of evidence was low for these conclusions (Table 4; see Appendixes F and G for study limitations) because many of the studies reporting on CIN had important study limitations (frequently lacking allocation concealment or blinding of participants and personnel), and the results were inconsistent. Overall, the studies had moderate heterogeneity, with an I-squared of 33 percent (p=0.07) (Figure 8). Using Harbord's modified test for small study effects, we found no evidence of asymmetry in the distribution of results by study precision (bias coefficient of -0.55, standard error of 0.96, p = 0.57).

For a variety of reasons, 8 of the RCTs reporting on CIN were not included in the meta-analysis (Appendix E, Evidence Table E-11).[124-131] One study did not report on CIN as an outcome, but did report on serum creatinine. The mean change in serum creatinine from baseline in this study did not meet any definition of CIN (Appendix E, Evidence Table E-12).

There were two observational studies, and they both reported the benefits of sodium bicarbonate administration to reduce CIN. A study by Tamai et al.[122] reported a significant difference in CIN for patients who received a high dose of sodium bicarbonate (833mEq/L) versus those who received a low dose (160 mEq/L). The study by Buhiraja et al.[123] showed a significant difference in CIN in patients who received sodium bicarbonate versus those who received normal saline. We did not factor the observational studies into the strength of evidence since the outcomes were in the same direction as the RCTs.

Other Outcomes

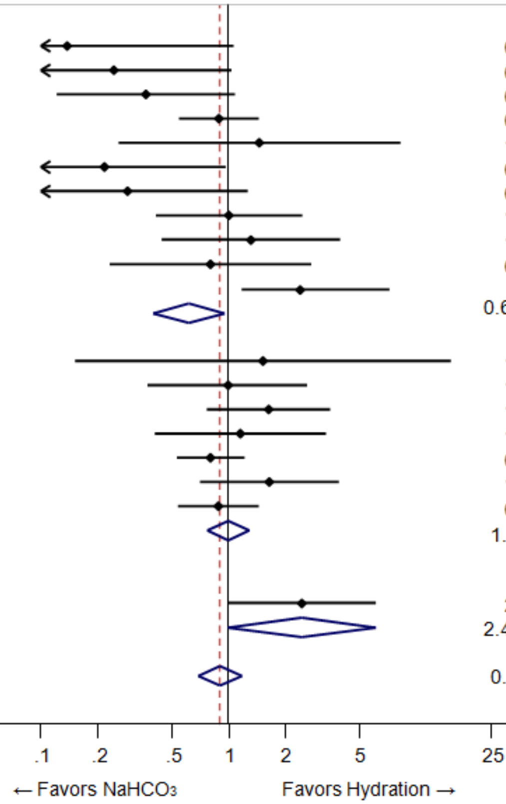
Of the studies that compared the risk of CIN using IV sodium bicarbonate with the risk of CIN using IV saline, 13 included data on secondary outcomes. Of these, 11 reported participants' needs for renal replacement therapy,[46,56,70,110-112,115-117,119,130] four reported on cardiac events,[56,70,114,115] three reported on hospitalization or length of stay,[110,112,120] and six reported on mortality.[110-112,115,117,120] (Appendix E; Evidence Table E-13). The overall strength of evidence was low that the mortality rates and the need for renal replacement therapy did not differ between IV sodium bicarbonate and IV saline (Table 4; see Appendixes F and G for study limitations). The studies addressing the need for renal replacement therapy and mortality had medium study limitations, were consistent in the direction of effect, and were imprecise, due to wide confidence intervals and small study populations. Only one study reporting on cardiac outcomes[114] reported a statistically significant difference between groups in favor of IV sodium bicarbonate (p=0.03). The remainder of the studies either reported statistically insignificant differences between groups or did not report statistics. The evidence was insufficient to determine whether or not cardiac events or length of hospitalizations differed between IV sodium bicarbonate and IV saline (Table 4; Appendix E, Evidence Table E-13).

Adverse events were reported in 11 studies. Data were only recorded if specific adverse events were reported or if the study reported no adverse events (Appendix E, Evidence Table E-14). Adverse events were not reported in a standardized manner and were rarely analyzed in these studies. As a result, we were unable to draw any firm conclusions as to whether or not the incidence of adverse events differed between IV sodium bicarbonate and IV saline.

Figure 8. Meta-analysis of IV sodium bicarbonate versus IV saline for the prevention of contrast-induced nephropathy

Author, year	Population	Contrast	CIN events, N (%) NaHCO3	CIN events, N (%) Hydration	RR (95% CI)
LOCM					
Merten, 2004[118]	CKD	Iopamidol	1 (1.67)	8 (13.56)	0.1 (0.0, 1.1)
Masuda, 2007[117]	CKD	Iopamidol	2 (6.67)	10 (34.48)	0.2 (0.1, 1.0)
Ozcan, 2007[56]	General	Ioxaglate	4 (4.55)	12 (13.64)	0.4 (0.1, 1.1)
Brar, 2008[111]	CKD	Ioxilan	25 (15.82)	30 (18.18)	0.9 (0.5, 1.5)
Vasheghani-Farahani, 2010[121]	CHF	Iohexol	3 (8.33)	2 (5.56)	1.5 (0.3, 8.3)
Motohiro, 2011[119]	CKD	Iopamidol	2 (2.56)	10 (12.99)	0.2 (0.0, 1.0)
Ueda, 2011[120]	CKD	Iopamidol, Iohexol	2 (6.67)	8 (27.59)	0.3 (0.1, 1.3)
Gomes, 2012[112]	CKD	Ioxaglate	9 (6.0)	9 (5.96)	1.0 (0.4, 2.5)
Boucek, 2013[110]	Diabetic/CKD	LOCM	7 (11.48)	5 (8.47)	1.3 (0.4, 3.9)
Kama, 2014[46]	High Risk	Iohexol	4 (11.11)	5 (14.29)	0.8 (0.2, 2.8)
Yeganehkhah, 2014[74]	High Risk	LOCM	20 (40.00)	7 (14.00)	2.9 (1.1, 6.6)
Subtotal (I-squared = 64.0%, p = 0.171)					0.65 (0.33, 1.25)
IOCM					
Ratcliffe, 2009[58]	General	Iodixanol	2 (10.53)	1 (6.67)	1.5 (0.2, 15.4)
Castini, 2010[36]	General	Iodixanol	7 (13.46)	7 (13.73)	1.0 (0.4, 2.6)
Lee, 2011[115]	Diabetic/CKD	Iodixanol	17 (9.04)	10 (5.35)	1.6 (0.8, 3.5)
Beyazal, 2014[109]	CKD	Iodixanol	6 (30.0)	5 (25.0)	1.2 (0.4, 3.3)
Thayssen, 2014[70]	Cardiac disease	Iodixanol	33 (18.23)	43 (23.76)	0.8 (0.5, 1.2)
Kooiman, 2014[114]	CKD	Iodixanol	14 (5.11)	8 (3.03)	1.7 (0.7, 3.9)
Manari, 2014[116]	Cardiac disease	Iodixanol	24 (16.55)	29 (19.21)	0.9 (0.5, 1.5)
Subtotal (I-squared = 0.0%, p = 0.902)					1.02 (0.70, 1.48)
Not Reported					
Koc, 2013[113]	Diabetic	Not Reported	15 (15.96)	6 (5.94)	2.5 (1.0, 6.1)
Subtotal (I-squared = .%, p = .)					2.45 (0.99, 6.09)
Overall (I-squared = 54.2%, p = 0.661)					0.93 (0.68, 1.27)

NOTE: Weights are from random effects analysis



Risk Ratio and 95% Confidence Intervals

%=percent; 1/2NS=0.45% saline; CHF=congestive heart failure; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; IOCM=iso-osmolar contrast media; LOCM=low-osmolar contrast media; N=sample size; $NaHCO_3$=sodium bicarbonate; NS=normal saline (0.9%); p=p-value; RR=risk ratio

Table 4. Summary of the strength of evidence: IV sodium bicarbonate versus IV saline

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN	RCT: 19 (3303)	Medium	Direct	Inconsistent	Precise*	Low	Low strength of evidence that IV sodium bicarbonate did not differ from IV saline in the risk of CIN
Development of CIN (in studies using LOCM)	RCT: 11 (1555)	Low	Direct	Inconsistent	Imprecise	Low	Low strength of evidence that IV sodium bicarbonate reduced the risk of CIN compared to IV saline in patients receiving LOCM
Development of CIN (in studies using IOCM)	RCT: 7 (1748)	Medium	Direct	Inconsistent	Imprecise	Low	Low strength of evidence that IV sodium bicarbonate did not differ from IV saline in the risk of CIN in patients receiving IOCM
Need for RRT	RCT: 11 (1558)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that the need for RRT did not differ between IV sodium bicarbonate and IV saline
Cardiac events	RCT: 4 (1468)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether cardiac events differed between IV sodium bicarbonate and IV saline
Mortality	RCT: 6 (1237)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that mortality rates did not differ between IV sodium bicarbonate and IV saline
Hospitalization, length of stay	RCT: 3 (480)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether length of hospitalization differed between IV sodium bicarbonate and IV saline

CIN=contrast-induced nephropathy; IV=IV; N=sample size; RCT=randomized controlled trial; RRT=renal replacement therapy
*The results were precise enough to rule out a clinically important increase in CIN with IV sodium bicarbonate.

N-Acetylcysteine Plus IV Saline Versus IV Sodium Bicarbonate

In previous sections, we briefly explained the physiologic basis for studying the use of N-acetylcysteine or IV sodium bicarbonate to prevent CIN, and we summarized the evidence on the effectiveness of each of these two interventions compared with IV saline alone. In this part of the analysis, we looked for evidence on head-to-head comparisons of these two interventions.

Study Characteristics

Our search identified seven RCTs[36,46,56,58,70,74,132] with a total study population of 1619 that compared N-acetylcysteine plus IV saline with IV sodium bicarbonate (number analyzed=930) and two observational studies.[97,133] Contrast media included iodixanol,[36,58,70] ioversol,[132] iohexol,[46,74] and ioxaglate.[56] Contrast media were administered intravenously in one study[46] and intra-arterially in the other six studies. The seven studies were completed between 2007 and 2014 and were conducted in the United States,[58] Italy,[36] Denmark,[70] Argentina,[132] Iran,[74] and Turkey.[46,56] The mean age of patients in these studies ranged from 59 to73. The study population for three of the RCTs included only individuals with kidney dysfunction.[36,56,132] The patients in one study[58] had kidney dysfunction alone (17%), diabetes mellitus alone (59%), or both (24%). Patients in the study by Kama, et al.[46] were considered to be at moderate or high risk of developing CIN (73% had an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or less). Only 8 percent of the patients in the study by Thayssen et al.[70] had an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2. The percentage of patients with diabetes mellitus ranged from 8.5 percent to 68 percent. The studies had a total follow up period of 48 hours to 30 days; the outcomes of CIN were reported at 48 hours;[56,74] at 48 to 72 hours;[46,70,132] at 24, 48, and 120 hours (5 days)[36] (personal communication with Diego Castini, April 28, 2014); and at 24, 48, and 168 hours (7 days).[58] (Appendix E, Evidence Tables E-1, E-3, E-15)

All studies compared N-acetylcysteine plus IV saline (sometimes in 5% dextrose in water) with IV sodium bicarbonate. However, in the studies by Thayssen[70] and Kama,[46] all arms also received IV normal saline.

Our search identified two observational studies[97,133] comparing N-acetylcysteine plus IV saline with IV sodium bicarbonate. There were 977 study participants. The first study was published in 2009 and was conducted in Israel,[133] and the other[97] was published in 2008 and conducted in the United States. The mean age of patients ranged from 60 to 71. All of the patients had comorbid disease at baseline in both studies.

Contrast-Induced Nephropathy

The incidence of CIN in the IV sodium bicarbonate groups ranged from 4.5 to 40.0 percent and from 4.7 to19.4 percent in the N-acetylcysteine plus IV saline groups. Three of the RCTs favored IV sodium bicarbonate, three favored N-acetylcysteine plus IV saline, and one was equivocal because it had very few CIN events[58] (Appendix E, Evidence Table E-16).

The overall pooled risk ratio for CIN in the RCTs comparing IV sodium bicarbonate with the combination of N-acetylcysteine and IV saline, using the Knapp-Hartung method, was 1.11 (95% CI: 0.51 to 2.41). The point estimate of the risk ratio indicates a very small increase in risk with sodium bicarbonate that was less than clinically important. The CI was too wide to rule out the possibility of either an important decrease or important increase in risk. The studies were inconsistent and had moderate heterogeneity, with an I-squared of 24 percent (Figure 9). The Harbord's modified test for small study effects did not show evidence of asymmetry in results by study precision (bias coefficient of -0.65, standard error of 1.80, p=0.735). The strength of evidence was insufficient to support a conclusion about the comparative effectiveness of these two interventions in the ability to prevent CIN (Table 5; Appendix E, Evidence Table E-16; see Appendixes F and G for study limitations).

Limitations of this comparison included the small number of studies, the varying regimens of fluid administration and N-acetylcysteine dosing, and the variations in follow up time. Four of the studies were exclusively in individuals with kidney disease (a population at higher risk for CIN), although the inclusion criteria were not exactly the same across all studies. One of the RCTs was conducted in individuals with either kidney dysfunction or diabetes mellitus. Another potential concern with the Ratcliffe, et al. study[58] was that only 66 percent of the participants completed the study.[58]

In the observational studies, the rate of CIN was similar in both groups' comparison groups. The results of the observational studies were similar to those reported in the RCTs regarding the comparison of the risk of CIN with N-acetylcysteine plus IV saline against IV sodium bicarbonate (Appendix E, Evidence Table E-16).

Other Outcomes

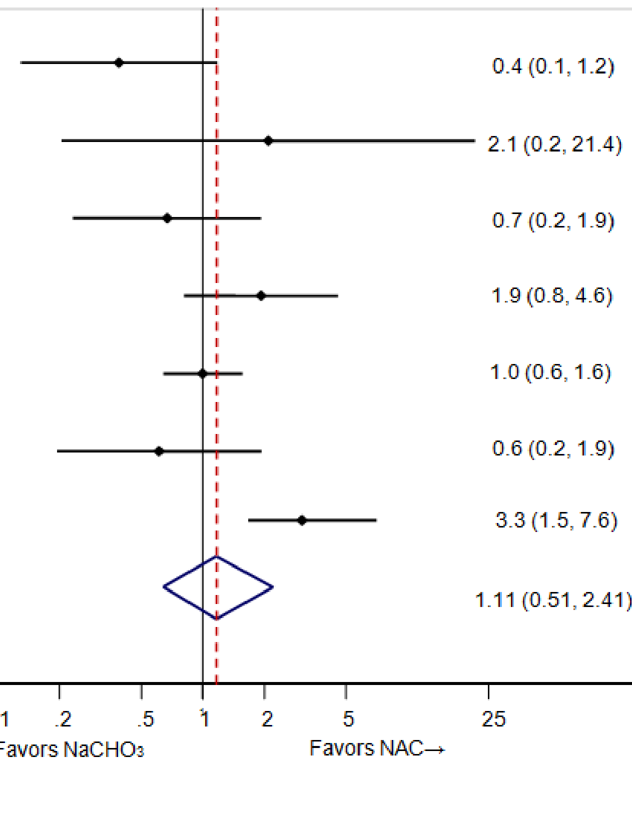
Of the seven RCTs that compared N-acetylcysteine plus IV saline with IV sodium bicarbonate for the development of CIN, five reported on secondary outcomes, including the need for renal replacement therapy, cardiac events, and mortality.[36,46,56,70,132] However, insufficient evidence existed to support firm conclusions about the comparative effects of N-acetylcysteine versus sodium bicarbonate for the outcomes of need for renal replacement therapy, cardiac events, or mortality (Table 5, see Appendixes F and G for study limitations). In those studies, no statistically significant difference was reported, no cases were reported, or statistics were not reported.

Although all of these studies reported on specific adverse events or reported that there were no adverse events, adverse events were not reported in a standardized manner, and were rarely analyzed. Thus, we were not able to draw any firm conclusions about whether or not the incidence of adverse events differed between N-acetylcysteine with IV saline and IV sodium bicarbonate (Appendix E, Evidence Table E-18).

Figure 9. Meta-analysis of N-acetylcysteine plus IV saline versus sodium bicarbonate for the prevention of contrast-induced nephropathy

Author, year	Population	$NaCHO_3$	NAC	CIN events, N (%) $NaHCO_3$	CIN events, N (%) NAC	RR (95% CI)
Ozcan, 2007[56]	Renal dysfunction	$NaHCO_3$	NAC + saline	4 (4.5)	11 (12.5)	0.4 (0.1, 1.2)
Ratcliffe, 2009[58]	Renal dysfunction or diabetes	$NaHCO_3$	NAC + saline	2 (10.5)	1 (4.7)	2.1 (0.2, 21.4)
Castini, 2010[36]	Renal dysfunction	$NaHCO_3$	NAC + saline	5 (9.6)	8 (15.0)	0.7 (0.2, 1.9)
Heguilen, 2013[132]	Renal dysfunction	$NaHCO_3$	NAC + saline	15 (35.7)	6 (15.8)	1.9 (0.8, 4.6)
Thayssen, 2014[70]	Cardiac issues	$NaHCO_3$ + saline	NAC + saline	33(18.2)	32(18.2)	1.0 (0.6, 1.6)
Kama, 2014[46]	High risk CIN	$NaHCO_3$ + saline	NAC + saline	4 (11.1)	7 (19.4)	0.6 (0.2, 1.9)
Yeganehkhah, 2014[74]	High Risk CIN	$NaHCO_3$ + saline	NAC + saline	20 (40.00)	6 (12.00)	3.3 (1.5, 7.6)
Overall (I-squared = 63.45%, p = 0.752)						1.11 (0.51, 2.41)

NOTE: Weights are from random effects analysis



%=percent; CI=confidence interval; N=sample size; NAC=N-acetylcysteine; $NaHCO_3$=sodium bicarbonate; p=p-value; RR=risk ratio

Table 5. Summary of the strength of evidence: N-acetylcysteine plus IV saline versus sodium bicarbonate

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN, short-term	RCT: 7 (930)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing CIN
Need for RRT	RCT: 4 (710)	Medium	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing the need for RRT
Cardiac events	RCT: 3 (613)	Medium	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing cardiac events
Mortality	RCT: 2 (442)	Medium	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from IV sodium bicarbonate in preventing mortality

CIN=contrast-induced nephropathy; IV=IV; N=sample size; RCT=randomized controlled trial; RRT=renal replacement therapy

Statins

In addition to decreasing low density lipoprotein cholesterol, statins have cholesterol-independent functionalities that play a growing role in various clinical contexts, including the prevention of both myocardial damage during percutaneous coronary intervention[134] and atrial fibrillation after cardiac surgery.[135] The proposed mechanism related to the prevention of CIN is that statins act as stabilizers of the endothelium and as free radical scavengers in a model of ischemic nephropathy.[136] Given the demonstrated pleiotropic nature of statins in clinical settings, it is important to evaluate the effect of statins on CIN as well as their effects on other outcomes.

Study Characteristics

Our search identified 19 RCTs[137-150] and one observational study on statins (Appendix E, Evidence Tables E-1, E-3, E-19).[151] The 19 RCTs included 10,574 participants. Eight studies compared statins with placebo,[138,139,144,145,152-155] one compared statin plus N-acetylcysteine plus sodium bicarbonate with N-acetylcysteine plus sodium bicarbonate,[137] and four compared statin plus N-acetylcysteine plus saline with N-acetylcysteine plus saline.[141,142,146,156] The remainder of the studies compared statin with statin,[143,148,149] statin plus saline with saline and chronic statin plus saline,[140] low-dose statin plus probucol with high-dose statin plus probucol,[150] and statin to statin plus probucol[147]. Contrast media used included iodixanol,[137,142-146] iopromide,[138,148] iobitridol,[139] iohexol,[140,143] and iopamidol.[141,147,150] Contrast media were administered intra-arterially in all studies.

These studies were completed between 1997 and 2015 and were conducted in Italy,[137,139,142,146] China,[138,143,145,147,150,153,157,158] Turkey,[140,141,148,154] Korea,[144,149,152] Iran,[155] and Egypt.[156] In all of the RCTs, the mean age of patients ranged from 54 to 76 years. The percentage of patients with chronic kidney disease at baseline ranged from 4 percent to 100 percent and the percent of patients with diabetes mellitus ranged from 15 percent to 100 percent (Appendix E, Evidence Tables E-1, E-3, E-19).

The observational study,[151] with a study population of 28,871, compared statin therapy prior to the procedure with the absence of statin therapy. The contrast media used were not specified but all were administered intra-arterially. This study was completed between 1997 and 2003 and was conducted in the United States. In this study, the mean age of patients was 64. The percentage of patients with chronic kidney disease was not specified, while the percentage of patients with diabetes mellitus was 30 percent (Appendix E, Evidence Tables E-1, E-3, E-19).

Contrast-Induced Nephropathy

We conducted two separate meta-analyses on the studies of statins to reduce the incidence of CIN in patients receiving intra-arterial contrast. One included eight studies on statin-naïve patients that compared statin plus IV saline with IV saline alone.[138,139,144,145,152-155] The other included five studies: four compared statins plus N-acetylcysteine plus IV saline with N-acetylcysteine plus IV saline,[141,142,146,156] and one compared statins plus N-acetylcysteine plus IV sodium bicarbonate with N-acetylcysteine plus IV sodium bicarbonate.[137] The remaining six studies were not included in the meta-analyses; they either included comparisons that were not similar enough to analyze[143,147-150] or did not include a CIN outcome.[140](Appendix E, Evidence Table E-20).

When evaluating the efficacy of prophylactic statin administration compared with IV fluids alone in the prevention of CIN, four studies[138,139,145,154] found both a statistically significant and clinically important reduction in CIN (above our 25% threshold for a minimally important difference) in the intervention arm. One study found a borderline clinically important difference.[144] Three studies did not show either a clinically or a statistically significant reduction.[152,153,155] The largest study of the group with positive findings (n=2998) found a significant reduction with statin administration in the general study population but not in the post-hoc subgroup analyses of statin naïve versus statin non-naïve participants.[145] This study had a high risk of bias based on the five criteria described in the methods for assessing risk of bias for individual studies (Appendix F), but its effect estimate was in the same direction as the other three studies in the meta-analysis (which had fewer study limitations). An additional study[142] evaluated the occurrence of CIN in the nonstandard time frame of 5 days and therefore was not included in the meta-analysis; this study did not demonstrate a clinically or statistically significant difference between the intervention and control arms (Figure 10).

In a meta-analysis of the eight studies with a CIN endpoint ranging from 48 to 72 hours after contrast media administration,[138,139,144,145,152-155] the pooled estimate of the effect of statin plus IV fluids compared with IV fluids alone demonstrated a clinically important but statistically insignificant reduced risk of CIN with statin use (pooled risk ratio 0.68; 95% CI: 0.39 to 1.20) . A sensitivity analysis demonstrated that no study unduly influenced the overall statistical significance of the pooled estimate, and a stratified analysis showed no substantial difference in estimation of effect by statin type, as the point estimates of effect were all clinically important. No statin type had a 95% CI that was fully in the range consistent with a clinically important effect The estimate for rosuvastatin, from four studies (risk ratio 0.69; 95% CI: 0.47 to 1.02) was clinically important, but the CI was wide enough to not rule out the possibility of an unimportant effect.[145,152,153,155] The estimate for atorvastatin, three studies (risk ratio 0.41; 95% CI: 0.02 to 2.71) was clinically important, but the CI was wide enough to not rule out the possibility of an unimportant effect. While the point estimate of the effect of simvastatin (risk ratio 0.75; 95% CI: 0.17 to 3.28) was not clinically important, the confidence interval was so wide that we cannot rule out the possibility of a clinically important benefit or harm. Note that atorvastatin was the only drug for which there was more than one study. A meta-regression was not conducted, due to the small number of studies. We saw no trends in the data that pointed to differences in groups by age, kidney function, diabetes status, or sex. The studies on statins had a medium risk of bias, and consistently showed a benefit in reducing CIN in favor of the statin drug with a relatively precise resulting estimate of the effect. Harbord's modified test for small study effects did not demonstrate evidence of asymmetry in results by study precision (bias coefficient of -1.49, standard error of 1.11, p=0.227). We concluded that the strength of evidence was low for demonstrating that a statin plus IV fluids was more effective than IV fluids alone at preventing CIN (Table 6; see Appendixes F and G for study limitations).

When evaluating the efficacy of statin administration plus N-acetylcysteine plus IV saline (or IV sodium bicarbonate) compared with N-acetylcysteine plus IV fluids (or IV sodium bicarbonate) in the prevention of CIN, four studies[137,141,146,156] found both a statistically significant and clinically important reduction in CIN (above our 25% threshold for a minimally important difference) in the statin arm. One study showed a statistically non-significant (p=0.86) reduction that was clinically insignificant.[142]

In a meta-analysis of studies with a CIN endpoint,[137,141,142,146] the pooled estimate of the effect of statin plus N-acetylcysteine plus IV fluids (saline or sodium bicarbonate) compared with N-acetylcysteine plus IV fluids (saline or sodium bicarbonate) demonstrated a clinically important and statistically significant reduced risk of CIN with statin use (pooled risk ratio 0.52;

95% CI: 0.29 to 0.93) with a number needed to treat of 18 (95% CI: 13.44 to 34.72) (see Figure 11). However, the CI for the risk ratio was wide enough that we cannot rule out the possibility of a clinically unimportant difference. A meta-regression was not conducted due to the small number of studies. We saw no trends in the data that pointed to differences in groups by age, kidney function, diabetes status, or sex. Harbord's modified test for small study effects did not demonstrate evidence of asymmetry in results by study precision (bias coefficient of -0.63, standard error of 1.68, p=0.735). We concluded that the strength of evidence was low for demonstrating that a statin plus N-acetylcysteine plus IV fluids was more effective than N-acetylcysteine plus IV fluids at preventing CIN, when considering study limitations, directness, consistency, and precision (Table 6; see Appendixes F and G for study limitations).

One study comparing atorvastatin to IV saline[140] did not report on CIN outcomes. This study reported on the change in serum creatinine and estimated glomerular filtration rate. No difference was reported in serum creatinine levels 48 hours after the procedure, and estimated glomerular filtration rate was significantly lower in the atorvastatin group 48 hours after the procedure (Appendix E, Evidence Table E-20).

Two studies reported on the incidence of CIN in participants receiving a statin versus a statin plus probucol.[147,150] Han, 2013[150] compared low-dose atorvastatin plus probucol with high-dose atorvastatin plus probucol as well as with high-dose atorvastatin. No significant difference in CIN incidence was found between the groups 48 hours after the procedure. Li, 2014[147] compared atorvastatin with atorvastatin plus probucol. No significant difference in CIN was reported between groups (Appendix E, Evidence Table E-20).

Three studies compared either different dosages of the same statin[143,149] or different statins.[148] Jo, 2014[149] found no significant difference between high-dose and low-dose atorvastatin in preventing CIN. Kaya, 2013[148] found no significant difference between atorvastatin and rosuvastatin in preventing CIN. Xinwei, 2009[143] found a significantly lower incidence of CIN in patients receiving high-dose simvastatin when compared with low-dose (Appendix E, Evidence Table E-20).

One observational study reported on statins versus IV saline and found a significant decrease in CIN in the group receiving statins.[151] The results were similar to those reported in the RCTs comparing statins with IV saline.

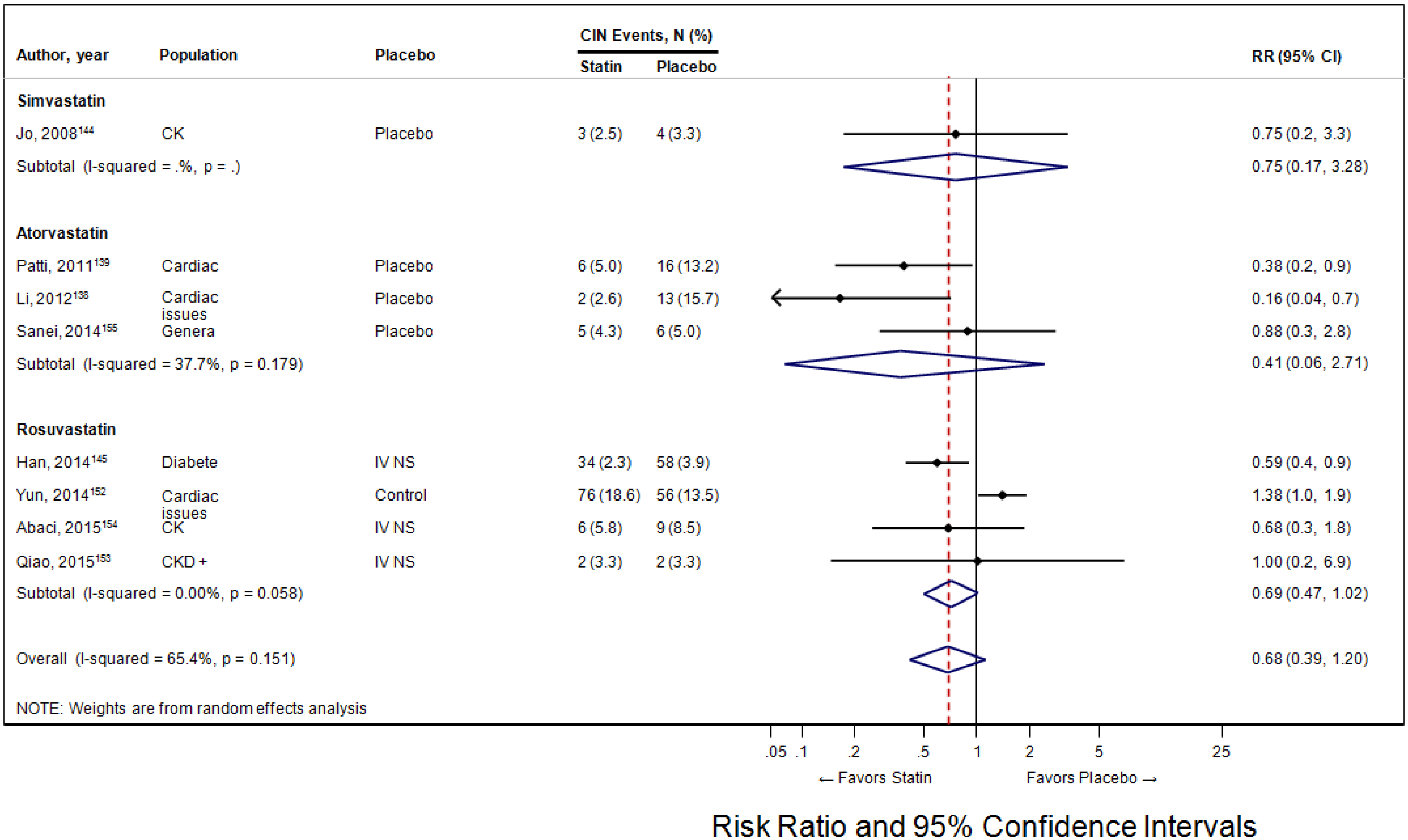
Four articles published in Chinese and one in Arabic were reviewed to determine if findings published in non-English language journals were different than those published in English-language journals. Three studies compared statins with IV saline and found significantly significant reductions in CIN in the statin intervention group[159,160] or higher estimated glomerular filtration rate in the statin group (statistical significance not reported).[161] These results were generally consistent with the English-language RCTs comparing statins with IV saline. One study compared low-dose statins with high-dose statins and found no significantly significant difference between groups.[162] Another compared rosuvastatin plus furosemide with furosemide and found no significant difference in CIN incidence between groups.[163]

Other Outcomes

Secondary outcome reporting was not consistent across studies. Need for renal replacement therapy was reported in three comparing statins to IV saline,[144,145,156] and three comparing statins plus N-acetylcysteine to N-acetylcysteine,[137,142,146] two comparing statins by dose of administration,[145,149] one comparing different statins.[157] One study comparing statins[157] and one comparing statin to IV saline reported on mortality.[145] Three comparing statins plus N-acetylcysteine to N-acetylcysteine, and one comparing statins by dose of administration[149] also reported on mortality. Only p-values were reported for need for renal replacement therapy and mortality and none reached a significance of p less than 0.05. Two studies reported on length of stay or hospitalization, both of which compared statins to IV saline.[139,144] One study showed no difference between groups while the other, Patti et al., 2011[139] showed a statistically significant difference (p=0.007) favoring the use of statins. Cardiac events were reported in five studies, two for statins versus IV saline,[145,157] two for statins plus N-acetylcysteine versus N-acetylcysteine,[146,156] and one compared statins by dose.[149] Statistical significance was reported only in the set of three studies comparing statins to IV saline. Two of these studies reported no statistically significant difference between groups,[146,164] and the other reported a statistically significant difference (p=0.02) in favor of statins.[145] Two studies comparing statins to IV saline reported on hospital length of stay reporting no comparisons between groups.[139,144] The strength of evidence was insufficient regarding whether or not statins had an impact on any of these secondary outcomes (Table 6; Appendix E, Evidence Table E-21; see Appendixes F and G for study limitations). No clinically important or statistically significant differences were seen in the need for dialysis; very few events were reported.[137,142,144-146,149,150,156,157] Five studies reported cardiac outcomes[145,146,149,156,157] and did not report consistently across outcomes. Of the six studies that reported mortality by intervention group, none showed a statistically significant or clinically important difference; the strength of evidence was insufficient, however, because very few deaths were reported, with results that were too imprecise and inconsistent.[137,142,145,146,149,157] The strength of evidence was insufficient to determine if statins were effective at reducing length of hospitalization (Table 6; Appendix E, Evidence Table E-21; see Appendix G for study limitations).[139,144]

Adverse events were reported in five studies. We were not able to draw any conclusions as to whether or not the incidence of adverse events differed between statins and IV fluids (Appendix E, Evidence Table E-22).[143]

Figure 10. Meta-analysis of statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy in patients receiving intra-arterial contrast

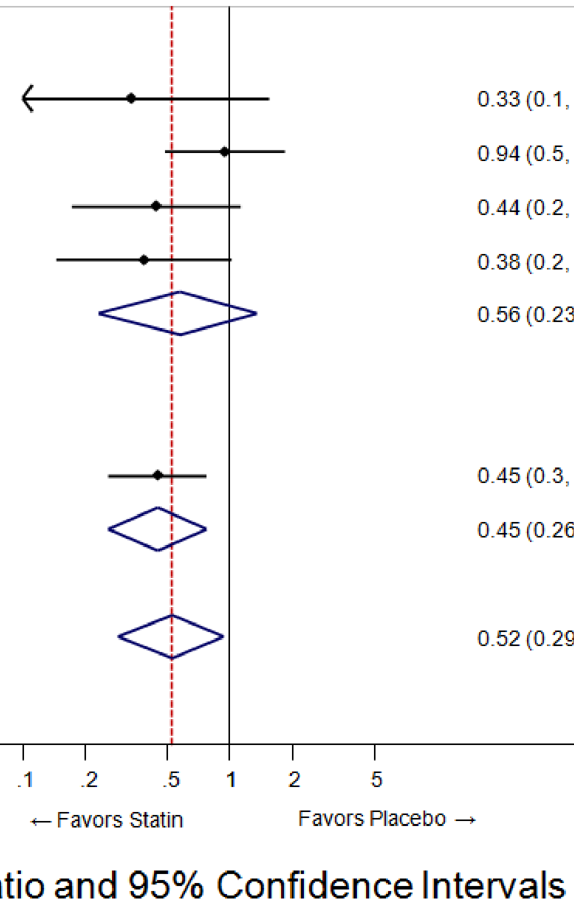


%=percent; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; IV=intravenous; N=sample size; p=p-value; RR=risk ratio

Figure 11. Meta-analysis of statins plus N-acetylcysteine plus IV fluids versus N-acetylcysteine plus IV fluids with or without placebo for the prevention of contrast-induced nephropathy in patients receiving intra-arterial contrast

Author, year	Population	Placebo	CIN Events, N (%) Statin	CIN Events, N (%) Placebo	RR (95% CI)
Atorvastatin + NAC					
Ozhan, 2010[141]	General	IV saline + NAC	2 (3.3)	7 (10.0)	0.33 (0.1, 1.5)
Toso, 2010[142]	CKD	IV saline + NAC	15 (9.9)	16 (10.5)	0.94 (0.5, 1.8)
Quintavalle, 2012[137]	CKD	Fluid + NAC	6 (3.0)	14 (6.7)	0.44 (0.2, 1.1)
Shehata, 2015[156]	CKD + DM + Cardiac	IV saline + NAC	5 (7.7)	13 (20.0)	0.38 (0.2, 1.0)
Subtotal (I-squared = 15.4%, p = 0.131)					0.56 (0.23, 1.38)
Rosuvastatin + NAC					
Leoncini, 2014[146]	Cardiac issues	IV saline + NAC	17 (6.7)	38 (15.1)	0.45 (0.3, 0.8)
Subtotal (I-squared = .%, p = .)					0.45 (0.26, 0.77)
Overall (I-squared = 3.8%, p = 0.036)					0.52 (0.29, 0.93)

NOTE: Weights are from random effects analysis



%=percent; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; N=sample size; NAC=N-acetylcysteine; $NaHCO_3$=sodium bicarbonate; p=p-value; RR=risk ratio

Table 6. Summary of the strength of evidence: statins plus IV fluids versus placebo with or without fluids and statins plus N-acetylcysteine versus N-acetylcysteine alone in patients receiving intra-arterial contrast

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN: statin + IV saline vs. IV saline (meta-analysis)	RCT: 8 (5024)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that statins plus IV fluids have a lower risk of CIN than IV fluids aloe.
Development of CIN: statin + NAC + IV saline or bicarbonate vs. NAC + IV saline or bicarbonate (meta-analysis)†	RCT: 5 (1477)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that statins plus NAC plus IV fluids (or bicarbonate) have a lower risk of CIN than NAC plus IV fluids (or bicarbonate)
Need for RRT (statins + IV saline vs. IV saline)	RCT 2 (3245)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence that statins plus IV fluids have a lower risk of renal replacement therapy than IV fluids alone.
Need for RRT (statin + NAC + IV saline or bicarbonate vs. NAC + IV saline or bicarbonate)	RCT: 3 (1017)	Medium	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence that statins plus NAC plus IV fluids (or bicarbonate) have a lower risk of renal replacement therapy than NAC plus IV fluids (or bicarbonate)
Mortality (statins + IV saline vs. IV saline)	RCT: 1 (2998)	High	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence that statins plus IV fluids have a lower risk of mortality than IV fluids alone.
Mortality (statin + NAC + IV saline or bicarbonate vs. NAC + IV saline or bicarbonate)	RCT: 3 (1017)	Medium	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence that statins plus NAC plus IV fluids (or bicarbonate) have a lower risk of mortality than NAC plus IV fluids (or bicarbonate)
Cardiac outcomes (statins + IV saline vs. IV saline)	RCT: 1 (2998)	High	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence that statins plus IV fluids have a lowers risk of cardiac outcomes than IV fluids alone.

Table 6. Summary of the strength of evidence: statins plus IV fluids versus placebo with or without fluids and statins plus N-acetylcysteine versus N-acetylcysteine alone in patients receiving intra-arterial contrast (continued)

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Cardiac outcomes (statin + NAC + IV saline or bicarbonate vs. NAC + IV saline or bicarbonate)	RCT: 1(304)	Medium	Direct	Only 1 study	imprecise	Insufficient	Insufficient strength of evidence that statins plus NAC plus IV fluids (or bicarbonate) have a lower risk of cardiac outcomes than NAC plus IV fluids (or bicarbonate)
Hospitalization, length of stay (statins + IV saline vs. IV saline)	RCT: 2 (488)	Low	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that statins plus IV fluids have a lower risk of increased length of hospital stay than IV fluids alone.

CIN=contrast-induced nephropathy; IV=intravenous; N=sample size; NA=not applicable; NAC=N-acetylcysteine; RCT=randomized controlled trial; RRT=renal replacement therapy

* Includes studies examined in meta-analysis because of comparability of intervention and control arms

†One study included in this meta-analysis compared statin + NAC + sodium bicarbonate + IV saline with NAC + sodium bicarbonate + IV saline.

Adenosine Antagonists Plus IV Saline Versus IV Saline

Elevated adenosine levels contribute to the pathophysiology of acute reductions in kidney function through the induction of renal vasoconstriction after contrast media exposure.[165] Adenosine antagonists belonging to the xanthine drug class, such as theophylline and aminophylline, could theoretically prevent CIN by intervening along this pathway. This would consequently preserve renal blood flow and glomerular filtration perfusion pressure.[166]

Study Characteristics

We found a total of five studies that reviewed the role of adenosine antagonists in the prevention of CIN: four examined theophylline,[31,68,167,168] and one examined aminophylline.[66] All five were RCTs. One[68] used IV contrast media and the others used contrast media that were administered intra-arterially.[31,66,167,168] Four studies used LOCM agents, [66,68,168 31] and one used IOCM.[167] All studies used IV saline prior to and after the procedure, and administered intervention drugs prior to and after the procedure. Two studies used elevated serum creatinine as an inclusion criterion,[31,167,168] one included only those with at least one risk factor for CIN,[168] one used coronary artery disease as an inclusion criterion,[66] and one included a population without kidney disease or diabetes mellitus.[68] The followup for all of the studies was between 48[31,66,167] and 72 hours[68,168] for CIN outcomes (Appendix E, Evidence Tables E-1, E-3, E-23).[31] The studies were published from 2008[68] through 2012.[168] (Appendix E, Evidence Tables E-1, E-3, E-23). Four of the studies had more than one important study limitation,[31,68] and one had low risk of bias based on the five criteria described in the methods for assessing risk of bias for individual studies (Appendix F).[168] Some of the studies had low scores for allocation generation,[31,68] allocation concealment,[31,66,68] masking of intervention,[31,66,68] and incomplete outcome reporting.[68,167]

We identified one observational study that compared an adenosine antagonist with IV saline in 52 patients.[169] The country of origin was not identified in this study. The average age ranged from 71 to 72, 44 percent of patients had diabetes mellitus, and all patients had been diagnosed with renal insufficiency.

Contrast-Induced Nephropathy

Regarding the intra-arterial administration of contrast media: the results of our primary analysis were mixed with regard to the incidence of CIN with adenosine antagonists plus IV saline compared with IV saline. Of the three studies that only examined theophylline against IV saline, two showed a clinically important increase in CIN in the theophylline group that was not statistically significant,[68,167] and one demonstrated a clinically important reduction in CIN in the theophylline group that was statistically significant.[168] Other studies compared intra-arterial administration of contrast media containing multiple comparison arms.[31,66] In the two studies with multiple comparisons, the arms involving the adenosine antagonists had less CIN than the IV saline arms; however, one study[31] examined theophylline in combination with N-acetylcysteine and not on its own (Figure 12).

In the meta-analysis exploring all studies involving a comparison between adenosine antagonists plus IV saline and IV saline alone, the confidence interval was so wide that we could not rule out a clinically important decrease or increase (pooled risk ratio with Knapp-Hartung method, 0.80; 95% CI: 0.01 to 44.48) (Figure 12). The strength of evidence was insufficient to support a conclusion about the effect of adenosine agonists on the risk of CIN because the study results were imprecise and inconsistent, and the study limitations were medium (Table 7; see Appendix G for study limitations).

Only one study[68] examined the effect of theophylline in a population for which contrast media was administered IV. It demonstrated a clinically important increased risk of CIN with theophylline that was not statistically significant (Figure 12).

One of the studies was not included in our meta-analysis.[31] It included N-acetylcysteine in one of the interventions and the p-value was calculated across the three arms (Appendix E, Evidence Table E-24).

The results of the observational studies were similar to those reported in the RCTs regarding the comparison of the risk of CIN with aminophylline versus IV saline.[169]

Other Outcomes

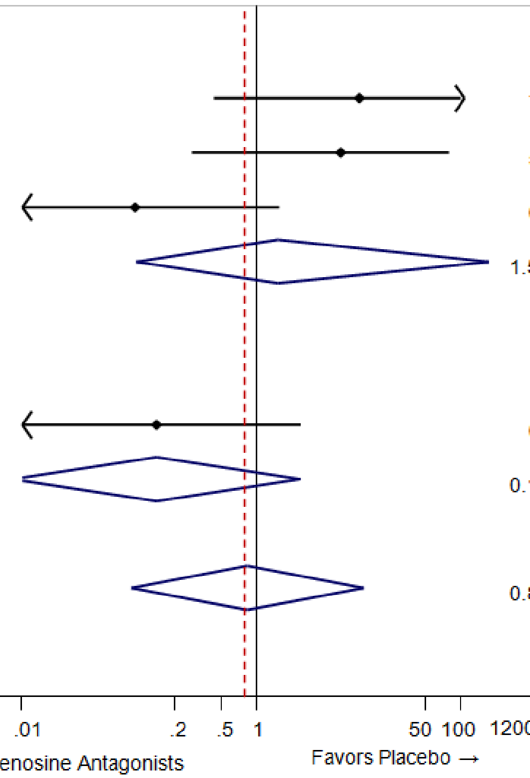
Four of the five studies reporting on adenosine antagonists reported on other outcomes. Two studies reported no events for the need for renal replacement therapy, cardiac events, mortality, and length of stay.[31,167] Two additional studies reported no cardiac events.[68,168] The strength of evidence was insufficient to determine the effect of adenosine antagonists on the need for renal replacement therapy, cardiac events, length of hospital stay or mortality (Table 7; Appendix E, Evidence Table E-25; see Appendix G for study limitations).

Adverse events were not reported in a standardized manner and were rarely analyzed, so we were unable to draw any conclusions around whether or not the incidence of adverse events differed between adenosine antagonists versus fluids (Appendix E, Evidence Table E-26).

Figure 12. Meta-analysis of adenosine antagonists plus IV saline versus IV saline for the prevention of contrast-induced nephropathy

Author, year	Population	Adenosine Antagonists	Placebo	CIN events, N (%) Adenosine Antagonists	CIN events, N (%) Placebo	RR (95% CI)
Theophylline + Saline						
Demir, 2008[68]	General	Theophylline	NS	4 (20.0)	0 (0.0)	7.6 (0.4, 132.5)
Matejka, 2010[167]	Renal dysfunction	Theophylline	NS	3 (9.68)	0 (0.0)	5.2 (0.3, 96.4)
Bilasy, 2012*[168]	Moderate risk for CIN	Theophylline	NS	0 (0.0)	6 (20.0)	0.1 (0.0, 1.6)
Subtotal (I-squared = 65.9%, p = 0.799)						1.56 (0.00, 1102.26)
Aminophylline + Saline						
Kinbara, 2010[66]	Cardiac Disease	Aminophylline	NS	0 (0.0)	4 (26.7)	0.1 (0.0, 2.4)
Subtotal (I-squared = .%, p = .)						0.14 (0.01, 2.39)
Overall (I-squared = 62.7%, p = 0.871)						0.80 (0.01, 44.48)

NOTE: Weights are from random effects analysis



Risk Ratio and 95% Confidence Intervals

%=percent; CI=confidence interval; CIN=contrast induced nephropathy; N=sample size; NS=normal saline (0.9%); p=p-value; RR=risk ratio

Table 7. Summary of the strength of evidence: adenosine antagonists plus IV saline versus IV saline

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN,* (meta-analysis)	RCT: 5 (3647)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the risk of CIN
Need for RRT	RCT: 2 (200)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the need for renal replacement therapy
Cardiac events	RCT: 4 (300)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the risk of cardiac events
Mortality	RCT: 2 (200)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on mortality
Length of stay	RCT: 2 (200)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of adenosine antagonists on the length of stay

CIN=contrast-induced nephropathy; N=sample size; RCT=randomized controlled trial; RRT=renal replacement therapy
* Includes studies examined in meta-analysis because of comparability of intervention and control arm

Renal Replacement Therapy Versus IV Fluids

Because contrast media clearance is usually delayed in an impaired kidney, hemodialysis and hemofiltration have been examined as possible methods for removing more IV contrast media in those with chronic kidney disease to reduce the risk of further kidney injury.[170,171] Studies demonstrate that 2 to 3 hours of hemodialysis effectively removes 60 to 90 percent of contrast media, but the clinical effects are not clear. Continuous venovenous hemofiltration is based on high-volume controlled hydration, which in theory reduces kidney exposure to the contrast media; however patients need to be in an intensive care setting for continuous monitoring.

Study Characteristics

Our search identified six RCTs on use of hemodialysis or hemofiltration with a total study population of 790 patients. These trials compared renal replacement therapy with IV fluids; four assessed the use of hemodialysis[59,172-174] and two assessed the use of hemofiltration.[175,176] All of the studies included patients with chronic kidney disease who were undergoing cardiovascular interventions. Only one study included patients undergoing additional procedures.[173] In all of the studies, contrast media included LOCM and was administered intra-arterially (two studies also administered it intravenously).[172,173] These studies were completed between 1998 and 2007 and were conducted in Germany,[59,172,174] Italy,[175,176] and Switzerland.[173] The mean age of patients ranged from 57 to 70. All studies included patients with different stages of chronic kidney disease at baseline; the percentage of patients with diabetes mellitus ranged from 23 to 64 percent.

Our search identified three observational studies with a total study population of 503 patients; these studies compared renal replacement therapy with IV fluids; one study assessed the use of hemodialysis[177] and two assessed the use of hemofiltration.[178,179] All studies included patients with chronic kidney disease who were undergoing cardiovascular interventions. Contrast media included LOCM in all studies and was administered intra-arterially in all studies. These studies were completed between 1991 and 2013 and were conducted in Japan[177,179] and Italy.[178] The mean age of patients ranged from 69 to 83. All studies included patients with different stages of chronic kidney disease at baseline, and the percentage of patients with diabetes mellitus ranged from 41 to 68 percent. Hemodialysis was started in all of the studies after the contrast media was administered, while hemofiltration was started before contrast media administration; some of the hemofiltration studies started hemofiltration both before and after contrast media administration, to evaluate the effects of timing[176,178] (Appendix E, Evidence Tables E-1, E-3, E-27). All studies had important study limitations based on the five criteria described in the methods for assessing risk of bias for individual studies (Appendix F).[176] All studies had an increased risk of bias because of the absence of blinding of the allocated intervention. Some studies were limited by problems with allocation generation,[59,172-174] allocation concealment,[59,172-174,175] and incomplete outcome reporting.[172,173,175]

Contrast-Induced Nephropathy

None of the studies on hemodialysis reported a statistically significant difference between the use of IV fluids and hemodialysis in preventing CIN.[172-174] The incidence of CIN was similar in both groups for all of the studies comparing hemodialysis and IV saline. The only study assessing hemodialysis plus IV glucose and saline[59] found that patients on hemodialysis had higher rates of CIN at 72 hours than those on IV saline only and those receiving N-acetylcysteine

(15.9% vs. 6.1% and 5.3%; p = 0.008), but this study also found that when the rate of CIN was reassessed thirty to sixty days later, this effect had disappeared. Because this study measured creatinine at time points that were different from the other studies, the studies were not comparable (Appendix E, Evidence Table E-27).[59] The pooled analysis using the Knapp-Hartung method for the three studies comparing hemodialysis with IV saline yielded a pooled risk ratio of 1.50, which is consistent with a clinically important increased risk (95% CI: 0.56 to 4.04, Figure 13).

The studies indicated that prophylactic hemodialysis does not prevent the incidence of CIN in patients with chronic kidney disease, regardless of the stage, the duration of the dialysis (from 2 to 4 hours), or the time between contrast media administration and initiation of dialysis. No benefit was found when hemodialysis was started before the contrast media was given.[174] The two studies that included results on contrast media clearance[172,174] demonstrated that peak levels of contrast media were lower in the hemodialysis group than in the control group during the initial hours after contrast media administration, but also showed that the effect of dialysis was no longer significant after 72 hours; after 72 hours, elimination half-life was comparable in both arms. This finding correlated with the lack of a clinical effect (Appendix E, Evidence Table E-29). The strength of evidence was low that hemodialysis does not reduce the risk of CIN and may even be harmful, because the effects of hemodialysis were consistent and direct but imprecise, the magnitude of effect was weak, and the study limitations were high (Table 8; see Appendixes F and G for study limitations).

The study by Frank et al.[174] was not included in the pooled analysis because it did not provide data for the incidence of CIN. It only reported an insignificant difference between arms (Appendix E, Evidence Table E-28).

The only observational study addressing this comparison showed that patients on hemodialysis had higher rates of CIN than those on IV saline, with a more harmful effect shown in those with more deteriorated renal function.[177]

The studies comparing hemofiltration with IV fluids reported that patients with severe chronic kidney disease may have a lower incidence of CIN. In these studies, this benefit was evident only when hemofiltration was started before contrast media administration. As Marenzi et al.[176] showed, when hemofiltration was started after the contrast media administration, its benefit was lost and the risk for developing CIN was comparable to patients receiving IV saline only. This effect was confirmed by the observational studies. While one RCT of hemofiltration included more than 50 patients with stage 3 to 4 chronic kidney disease per arm and the other RCT included about 30 patients per arm with severe chronic kidney disease, the conclusions were similar (Appendix E, Evidence Table E-29). The Harbord's modified test for small study effects did not show evidence of asymmetrical effects by study size (bias coefficient of 4.36, standard error of 5.90, p=0.595).

The evidence was insufficient to determine whether or not hemofiltration reduced the risk of CIN in patients with pre-existing severe chronic kidney disease, because of high study limitations, small study size, and the concern that both studies were from the same authors (i.e., they were not independently replicated). The hemofiltration studies were not combined with the hemodialysis studies in the pooled analysis due to their different designs.

Other Outcomes

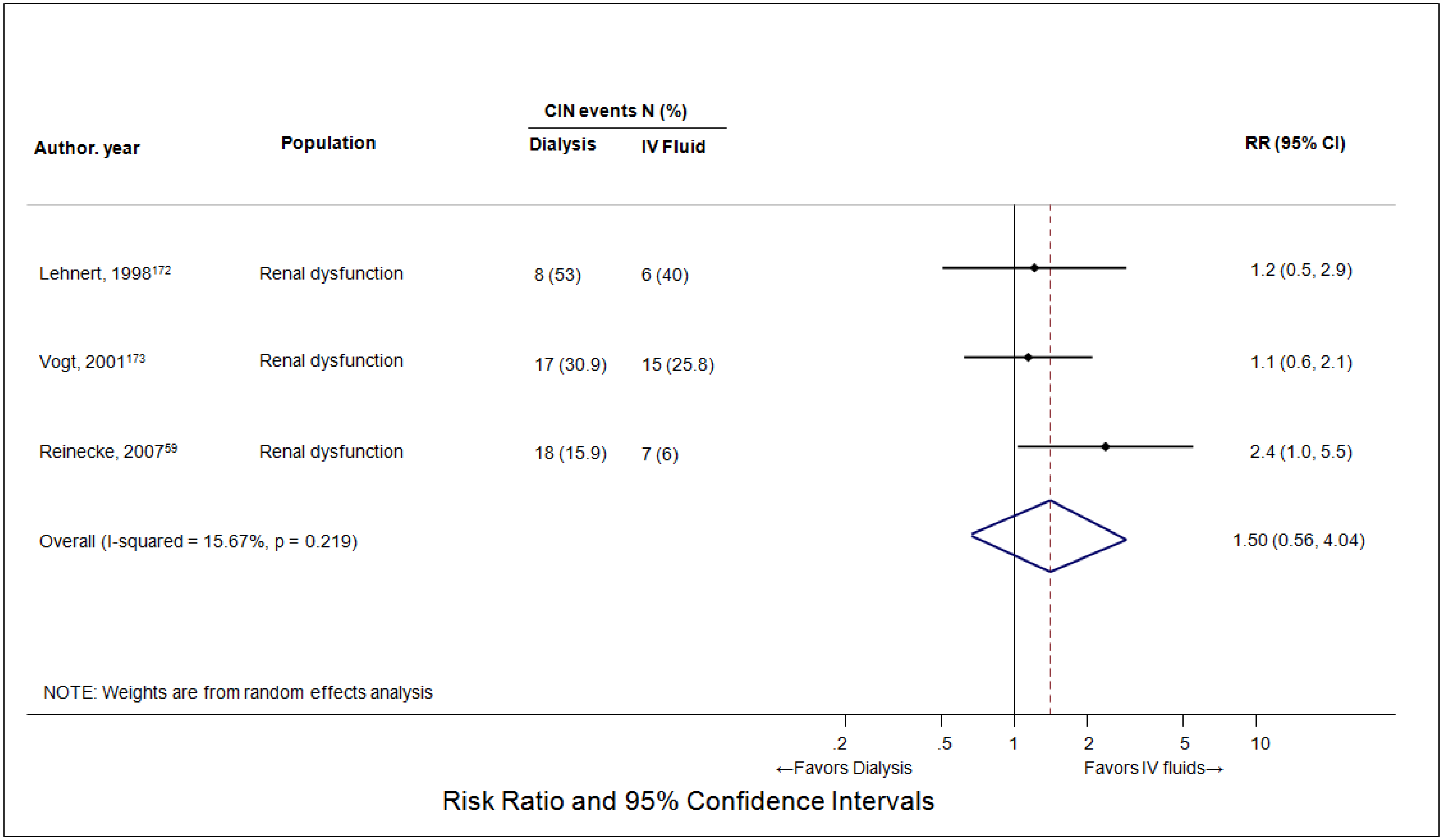
Five of the studies on renal replacement therapy reported on other outcomes.[173-176] Four reported on the need for renal replacement therapy; two hemodialysis studies,[59,173] and two hemofiltration studies [175,176] Three reported on cardiac outcomes; two hemodialysis studies[173,174] and one hemofiltration studies.[176] Four reported on mortality; Two hemodialysis studies,[59,173] and two hemofiltration studies.[175,176]

The studies comparing hemofiltration with IV saline demonstrated that patients may benefit from hemofiltration because they have a lower risk of emergency renal replacement therapy (18% vs. 0%, p <0.001),[175] or further renal replacement therapy (25% vs. 3%, p< 0.001[175] and 30% vs. 10%, p=0.02[176]), and lower risk for mortality (14% vs. 2%, p=0.02).[175] This benefit was evident only when hemofiltration was started before contrast media was administered. As Marenzi et al.[176] showed, when hemofiltration was started after the administration of contrast, its benefit was lost and the risk for developing CIN was comparable to those patients receiving hydration only. This finding was supported by Spini et al.,[178] who found a higher overall mortality for the patients who had continuous renal replacement therapy only after contrast media administration (57% vs. 16%, p=0.009; Appendix E, Evidence Table E-29). There was, however, a limitation to this group of studies; the studies that compared hemofiltration versus IV fluids were confounded by the use of IV bicarbonate with the hemofiltration. Insufficient evidence was available to support a conclusion about whether hemofiltration reduces the need for renal replacement therapy (Table 8).

The strength of evidence also was insufficient to determine whether renal replacement therapy (either hemofiltration or hemodialysis) reduces the risk of other outcomes due to the heterogeneity of the studies, comparators, and outcomes measured (Table 8; see Appendix G for study limitations).

Adverse events were reported in five studies (Appendix E, Evidence Table E-30).[59,173-176] The main adverse events reported were hematomas, blood loss, urinary retention, and/or anuria. Adverse events were not reported in a standardized manner and they were rarely analyzed in these studies, so we were unable to draw any conclusions regarding whether or not the incidence of adverse events differed between patients receiving renal replacement therapy and those who did not.

Figure 13. Meta-analysis of hemodialysis versus IV fluids for the prevention of contrast-induced nephropathy



%=percent; CI=confidence interval; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; IV=intravenous; LOCM=low-osmolar contrast media; N=sample size; P=p-value; RR=risk ratio

Table 8. Summary of the strength of evidence: renal replacement therapy versus fluids

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN HD studies	RCT: 4 (584)	High	Direct	Consistent	Imprecise	Low*	Low strength of evidence that hemodialysis does not decrease the risk of CIN compared with IV fluids
Development of CIN HF studies	RCT: 2 (206)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence that hemofiltration does not decrease the risk of CIN compared with IV fluids
Need for RRT HD studies	RCT: 2 (504)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that hemodialysis does not decrease the need for renal replacement therapy compared with IV fluids
Need for RRT HF studies	RCT: 2 (230)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that hemofiltration does not decrease the need for renal replacement therapy compared with IV fluids
Cardiac events HD studies	RCT: 2 (526)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that hemodialysis does not decrease the risk of cardiac outcomes compared with IV fluids
Cardiac events HF studies	RCT: 1 (113)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence that hemofiltration does not decrease the risk of cardiac outcomes compared with IV fluids
Mortality HD studies	RCT: 2 (504)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that hemodialysis does not decrease the risk of mortality compared with IV fluids
Mortality HF studies	RCT: 2 (130)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence that hemofiltration does not decrease the risk of mortality compared with IV fluids

CIN=contrast-induced nephropathy; HD=hemodialysis; HF=hemofiltration; RCT=randomized controlled trial; RRT=renal replacement therapy
*The strength of evidence was graded as low rather than insufficient because the results were precise enough to rule out a clinically important benefit. The results were not precise enough to determine if hemodialysis produced an increase or no difference in the risk of CIN.

Ascorbic Acid Versus IV Fluids

Contrast media causes vasoconstriction, hypoperfusion, and hypoxia with generation of reactive oxygen species, which results in indirect injury and further vasoconstriction. As an antioxidant, ascorbic acid acts as a scavenger of reactive oxygen species, reducing oxidative stress and possibly preventing CIN.[180,181]

Study Characteristics

Our search identified eight RCTs with a total study population of 1930 patients that compared the use of ascorbic acid with various hydration regimens and other interventions used to prevent CIN.[34,182-188] All of these studies included patients undergoing cardiovascular interventions using intra-arterial LOCM. These studies were completed between 2004 and 2013 and were conducted in Germany,[34,182] Canada,[184] China,[185] Italy,[187] Korea,[188] Saudi Arabia[186] and Slovenia.[183] The mean age of patients ranged from 61 to 74. The percentage of patients with diabetes mellitus ranged from 26 to 83 percent, and all studies included patients with mild or moderate chronic kidney disease but excluded patients with end-stage renal disease or those requiring hemodialysis.

Six studies compared the combination of ascorbic acid and IV fluids with IV fluids alone.[34,182-186] two of these studies added an N-acetylcysteine arm to the comparison,[34,186] and two studies only compared ascorbic acid with N-acetylcysteine added to hydration.[187,188]

In all eight studies, ascorbic acid was started prior to contrast media administration, with the total doses ranging from 1 gram as a unique dose[182] or split between two doses[34] to 7 grams split between three doses within 24 hours of contrast.[183-188] (Appendix E, Evidence Tables E-1, E-3, E-31).

Two studies had medium risk of bias,[183,185] and six had low risk of bias based on the five criteria described in the methods for assessing risk of bias for individual studies (Appendix F).[34,182,184,186-188] The limitations were due to problems with allocation generation,[182,183,185] allocation concealment,[183,185,188] and lack of blinding regarding the allocated intervention.[183,185,186]

Contrast-Induced Nephropathy

Six studies were included in our meta-analysis comparing ascorbic acid to IV saline.[34,182-186] The studies excluded from the meta-analysis included those using N-acetylcysteine in the intervention and in the control arm. (Appendix E, Evidence Table E-31) When evaluating the efficacy of prophylactic ascorbic acid administration against IV fluids alone in the prevention of CIN. Four studies[34,183,184,186] found a reduction of CIN in the intervention arm; three found this reduction to be clinically important (beyond our 25% threshold for a minimally important difference).[183,184,186] The remaining two studies found a slight but statistically insignificant increase of CIN in the intervention arm (6.7% vs. 4.3%[182] and 6.3% vs. 5.4%[185]).

Three studies compared ascorbic acid directly with N-acetylcysteine.[34,186,188] A fourth study incorporated N-acetylcysteine into the treatment regimen of all arms.[187] While one of the three studies found a statistically insignificant increase in CIN with the use of ascorbic acid (4.4% vs. 1.2%)[188] the other two showed a slight decrease in CIN incidence in the ascorbic acid arm (24.5% vs. 27.6% [34] and 3.6% vs. 8.5%[186]). When ascorbic acid was added to N-acetylcysteine, ascorbic acid slightly increased the risk of CIN when compared with N-acetylcysteine alone (10.3% vs. 9.9%[187] and 9.1% vs. 8.5%[186]).

In the meta-analysis using the Knapp-Hartung method, the pooled estimate of the effect of ascorbic acid plus IV fluids compared with IV fluids alone[34,182-186] demonstrated a statistically insignificant but clinically important reduced risk of CIN with ascorbic acid use (pooled risk ratio 0.72; 95% CI: 0.48 to 1.01) (Figure 14) A meta-analysis using the Knapp-Hartung method showed a clinically unimportant decrease in CIN in the ascorbic acid group (RR: 0.89; 95% CI: 0.34 to 2.30).(Figure 15). Our review showed no substantial difference in stratified analyses by study inclusion criteria for baseline kidney function. Harbord's modified test for small study effects did not demonstrate evidence of asymmetry in results by study precision for ascorbic acid plus IV fluid versus compared with IV fluid alone (bias coefficient of 0.39, standard error of 0.76, p =0.63). The Harbord's modified test for ascorbic acid compared with N-acetylcysteine had similar results (bias coefficient of 0.41, standard error of 1.62, p=0.843). The dose or timing of the intervention did not affect the results.

The strength of evidence was low for demonstrating that ascorbic acid plus IV fluids did not have a clinically important effect in preventing CIN compared with IV fluids alone, when considering study limitations, directness, consistency, and precision (Table 9; see Appendixes F and G for study limitations).

Other Outcomes

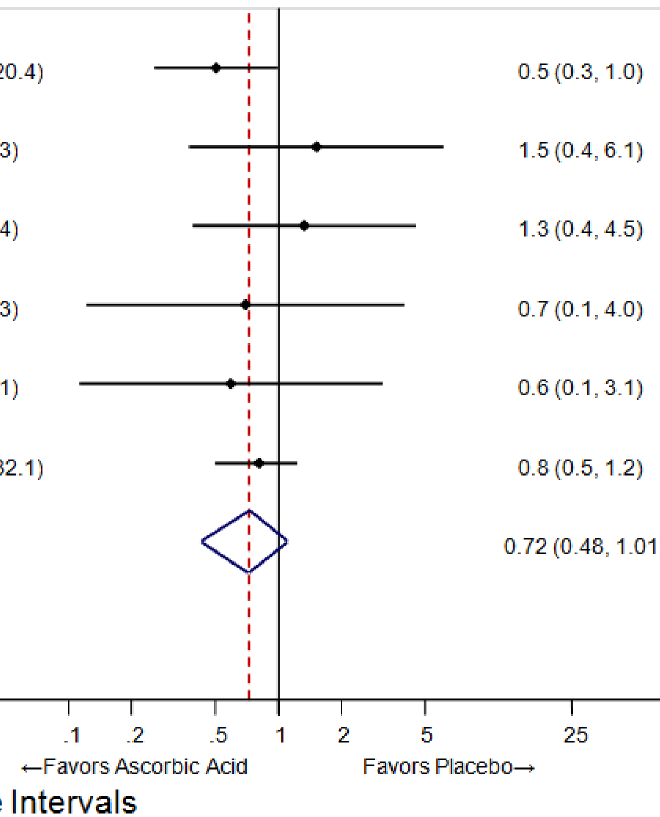
Other outcomes were reported in four of the studies on ascorbic acid: three on renal replacement therapy,[183,187,188] three on cardiac outcomes,[183,185,188] one on mortality,[188] and one on length of stay.[185] No clinically important or statistically significant differences were seen in the need for dialysis, but very few events were reported.[183,187,188] Findings were similar in the studies reporting on cardiac outcomes.[183,185,188] The study reporting on mortality very few deaths were reported.[187,188] There was insufficient evidence to determine if ascorbic acid was more effective than N-acetylcysteine at reducing the need for renal replacement therapy, reducing mortality, or cardiac events. The strength of the evidence was low that ascorbic acid was more effective than IV saline at reducing the need for renal replacement therapy or cardiac events, and insufficient to determine if there was an impact on length of hospitalization (Table 9; Appendix E, Evidence Table E-31; see Appendixes F and G for study limitations).

The absence of adverse events was reported only in two studies. We were not able to draw any conclusions about the incidence of adverse events based on those two reports. (Appendix E, Evidence Table E-34).

Figure 14. Meta-analysis of ascorbic acid versus IV fluids for the prevention of contrast-induced nephropathy

Author, year	Population	Ascorbic Acid	Placebo	CIN events, N (%) Ascorbic Acid	CIN events, N (%) Placebo	RR (95% CI)
Spargias, 2004[184]	CKD	AA + NS	Placebo + NS	11(9.3)	23(20.4)	0.5 (0.3, 1.0)
Boscheri, 2007[182]	CKD	AA + NS	Placebo + NS	5(6.8)	3(4.3)	1.5 (0.4, 6.1)
Zhou, 2012[185]	CKD	AA + NS	NS	6(7.3)	4(5.4)	1.3 (0.4, 4.5)
Dvorsak, 2013[183]	CKD	AA + NS	Placebo + NS	2(5.0)	3(7.3)	0.7 (0.1, 4.0)
Albabtain, 2013[186]	Diabetes or CKD	AA + NS	NS	2(3.5)	4(6.1)	0.6 (0.1, 3.1)
Brueck, 2013[34]	CKD	AA + NS	Placebo + NS	24(24.5)	62(32.1)	0.8 (0.5, 1.2)
Overall (I-squared = 0.0%, p = 0.099)						0.72 (0.48, 1.01)

NOTE: Weights are from random effects analysis

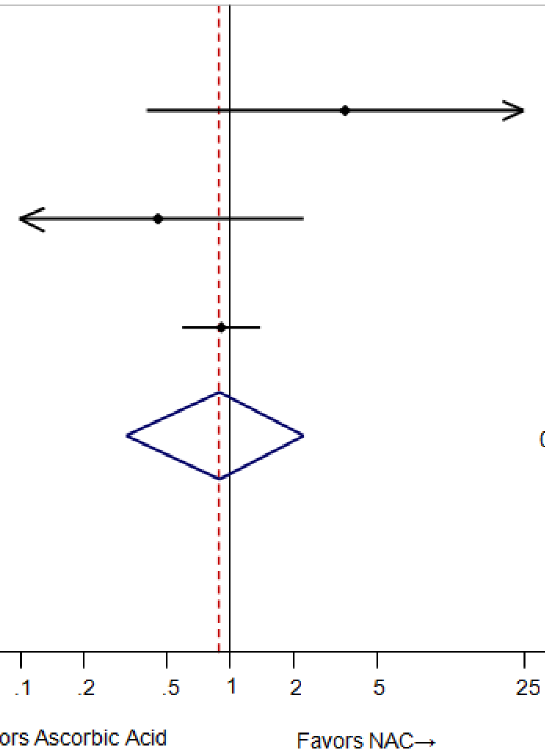


%=percent; AA=ascorbic acid; CI=confidence interval; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; LOCM=low-osmolar contrast media; N=sample size; NS=normal saline; P=p-value; RR=risk ratio

Figure 15. Meta-analysis of ascorbic acid versus N-acetylcysteine for the prevention of contrast-induced nephropathy

Author, year	Population	Ascorbic Acid	NAC	CIN events, N (%) Ascorbic Acid	CIN events, N (%) NAC	RR (95% CI)
Jo, 2009[188]	CKD	AA + H	NAC + H	4 (4.40)	1 (1.20)	3.5 (0.4, 31.0)
Albabtain, 2013[186]	CKD	AA + H	NAC + H	2 (3.51)	5 (8.06)	0.5 (0.1, 2.3)
Brueck, 2013[34]	CKD	AA + H	NAC + H	24 (24.5)	53 (27.6)	0.9 (0.6, 1.4)
Overall (I-squared = 16.36%, p = 0.651)						0.89 (0.34, 2.30)

NOTE: Weights are from random effects analysis



Risk Ratio and 95% Confidence Intervals

%=percent; AA=ascorbic acid; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; H=hydration; NAC=N-acetylcysteine; p=p-value; RR=risk ratio

Table 9. Summary of the strength of evidence: ascorbic acid versus IV saline

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Strength of Evidence	Summary of Key Outcomes
Development of CIN, ascorbic acid plus IV saline versus IV saline (meta-analysis)	RCT: 6 (1387)	Low	Direct	Inconsistent	Imprecise	Low	Low strength of evidence that ascorbic acid plus IV saline does not have a clinically important benefit in preventing CIN compared with IV saline alone
Development of CIN, ascorbic acid versus N-acetylcysteine (meta-analysis)	RCT: 3 (583)	Low	Direct	Inconsistent	Imprecise	Low	Low strength of evidence that ascorbic acid does not have a clinically important benefit in preventing CIN compared with N-acetylcysteine
Need for RRT (ascorbic acid plus IV saline versus IV saline)	2 (397)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that ascorbic acid does not differ from IV saline alone in preventing need for renal replacement therapy
Need for RRT (ascorbic acid versus N-acetylcysteine)	RCT: 1 (212)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence to determine if ascorbic acid does not differ from N-acetylcysteine in preventing need for renal replacement therapy
Cardiac events (ascorbic acid plus IV saline versus IV saline)	RCT: 2 (237)	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that ascorbic acid does not differ from IV saline alone in preventing cardiac outcomes
Cardiac events (ascorbic acid versus N-acetylcysteine)	1 (212)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence to determine if ascorbic acid does not differ from N-acetylcysteine in preventing cardiac outcomes
Mortality (ascorbic acid versus N-acetylcysteine)	RCT: 1 (212)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence to determine if ascorbic acid does not differ from N-acetylcysteine in preventing mortality
Hospitalization, length of stay (ascorbic acid plus IV saline versus IV saline)	1 (156)	Medium	Direct	Only 1 study	Imprecise	Insufficient	Insufficient strength of evidence to determine if ascorbic acid does not differ from IV saline alone in length of hospital stay

CIN=contrast-induced nephropathy; IV=IV; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy

Miscellaneous Comparisons

Many studies identified in our search did not fall into any of the main comparison groups listed above. We identified these comparisons as miscellaneous and categorized them into the following groups: N-acetylcysteine versus other interventions; sodium bicarbonate versus other interventions; N-acetylcysteine plus sodium bicarbonate versus other interventions; diuretics versus other interventions; vasoactive drugs versus other interventions; antioxidants versus fluids; dopamine versus other interventions; and head-to-head comparisons of different regimens for giving fluids. We summarized the findings of these miscellaneous comparisons below. All studies investigated the impact of the interventions on CIN. Full details are in Appendix H, Miscellaneous Comparisons, and Appendix I, Evidence Tables for Miscellaneous Comparisons.

N-Acetylcysteine Versus Other Interventions

We found 24 studies comparing N-acetylcysteine with other interventions including ascorbic acid,[34,187] nebivolol,[72] atorvastatin,[141] aminophylline,[66] theophylline,[31,68,189] fenoldopam,[28,190,191] misoprostol,[68] IV fluids,[58,59,126,132] allopurinol,[90] and dialysis. [43] There was substantial heterogeneity across these studies in terms of: dose of N-acetylcysteine; dose, type and duration of IV fluids; sample size; and follow-up period. The definition of CIN varied across studies as well. Because of the large heterogeneity of studies, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Sodium Bicarbonate Versus Other Interventions

We found four studies comparing sodium bicarbonate with other interventions not involving N-acetylcysteine.[124,127,129,192] The comparison interventions included acetazolamide,[129] long-term versus short-term sodium bicarbonate,[129] IV sodium bicarbonate versus oral sodium bicarbonate,[124] and saline versus saline plus sodium bicarbonate. Two studies used IOCM, two used LOCM, and one used both LOCM and IOCM. There was considerable heterogeneity across studies in terms of dose of sodium bicarbonate, dose and duration of other comparators, sample size, and follow-up period. All studies with the exception of one defined CIN as an increase of serum creatinine of 25% or at least 0.5 mg from baseline. Because of the large heterogeneity of studies, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

N-Acetylcysteine Plus Sodium Bicarbonate Versus Other Interventions

We found eight studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions, six RCTs,[58,128,132,187,193,194] and 2 observational.[58,128,132,187,193-196] In all studies, sodium bicarbonate was given IV at 3 ml/kg/hour or at 1 ml/kg/hour, before and after contrast media administration. A total of two doses of N-acetylcysteine was given prior to and after contrast media administration. All studies used IOCM. However, two studies also included administration of LOCM. N-acetylcysteine plus sodium bicarbonate was compared to N-acetylcysteine plus normal saline,[128,187] Renal Guard,[193] sodium bicarbonate plus dextrose,[132] or sodium bicarbonate alone.[194] The study population for all trials was comprised of patients with renal dysfunction who were undergoing coronary interventions or another major arteriographic procedure, and three of the studies only included patients with Stage 3 or Stage 4 chronic kidney disease.[132,193,194] Due to the substantial heterogeneity of the comparators, and follow-up periods, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Diuretics Versus Other Interventions

We found three studies comparing the use of different diuretics (furosemide, mannitol, and acetazolamide) in combination with IV saline to prevent CIN.[17,129,197] All studies included patients undergoing cardiovascular interventions and all studies included patients with diabetes mellitus. Two studies used LOCM and one used IOCM. Two studies evaluated furosemide as the diuretic of interest.[17,197] These two studies used it as a single comparator[17,197] Diuretic administration was given IV in all of the studies, but the protocols and doses varied. One study evaluated the effects of mannitol,[17] and another included acetazolamide. Due to the substantial heterogeneity of the comparators, and follow-up periods, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Vasoactive Agents Versus Other Interventions

We found 13 studies comparing vasoactive agents to other interventions: 12 RCTs,[28,68,72,190,191,198-204] and 1 observational;[205] four studies on fenoldopam;[28,190,191,198] two on calcium antagonists (one with nifedipine),[68] one with the combination of amlodipine and valsartan, an angiotensin receptor blocker)[202]; one on benazepril (an angiotensin converting enzyme inhibitor),[201] and one on nevibolol (a beta blocker).[72] We also include in this section two studies that investigated the need for suspending the use of an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker before receiving contrast media.[203,204] One study included only patients undergoing CT imaging,[68] and the remainder of the studies included patients undergoing cardiovascular interventions. All studies included patients with diabetes mellitus, but only one performed subgroup analysis for this population.[191] Four studies use LOCM, three used IOCM, and one used both IOCM and LOCM. The studies were very heterogeneous, from the medications included to the doses used. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Antioxidants Versus Hydration

We found seven studies evaluating different antioxidant strategies for preventing CIN. The antioxidant probucol was evaluated in two of these studies,[206,207] while two investigated pentoxifylline, an antioxidant and anti-inflammatory agent,[208,209] and the other two investigated sodium-2 mercaptoethanesulfonate (MESNA), a scavenger of reactive oxygen species,[210] zinc, which has the potential to act as an “endogenous antioxidant” via increasing metallothionein,[50] and trimetazidine, an antianginal agent which decreases free radicals, decreases oxygen consumption and may also decrease renal ischemia.[211] All were conducted in patients with impaired renal function (serum creatinine greater than 1.2 and less than 3.0 mg/dl) undergoing coronary interventions and receiving LOCM. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Fluid Interventions

We found 13 studies comparing different fluid regimens.[86,87,116,124,212-220] Notably, two studies compared fluids to no fluids, with one comparing 0.45% saline[214] and the other investigating normal saline.[217] Four compared oral fluids to IV normal saline,[87,124,215,220] and three compared isotonic saline to hypotonic saline.[216,218,219] Two studies compared standard dose IV normal saline to high-dose IV normal saline.[86,116] The timing of hydration, whether prior to or after the procedure, was compared in two studies.[212,217] Saline was separately compared with dextrose or sodium bicarbonate in three studies.[87,216,217] One study compared standard IV hydration to a left ventricular end diastolic pressure guided hydration protocol.[213] All of these studies defined CIN as an increase in serum creatinine by 25 percent or a change in serum creatinine of 0.5mg from baseline at 48 or 72 hours. However, one study also used an increase of glomerular filtration rate from a baseline of 50 percent,[212] while another study recorded any CIN event between one to four days. [213] A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Dopamine Versus Other Interventions

We found three studies assessing the effectiveness of dopamine in reducing CIN in patients with impaired renal function; two RCTs,[221,222] and one observational study[223] One of the studies compared dopamine and a placebo,[222] and another compared a combination of dopamine and furosemide to a combination of dopamine, furosemide, mannitol, and saline.[224] The remaining study had three arms that compared dopamine, saline, and aminophylline.[221] In all of the studies, dopamine was administered prior to and after contrast media administration. In two of the studies, the dose of dopamine was 2.5 micrograms/kg/min,[221,222] and the other study used a dose of 3 micrograms/kg/ml.[224] One study had no definition set for CIN,[224] while the other studies defined CIN as a change in serum creatinine greater than or equal to 25 percent or greater than 0.5 mg from baseline. A more detailed description of studies in this group and a summary of outcomes can be found in Appendixes H and I.

Discussion

We performed a comprehensive review of all major interventions to prevent CIN that are explored in the literature. In this section, we highlight the interventions for which evidence of a clinically important benefit is strongest and provide commentary on the limitations of the evidence as well as the manner in which our results compare with the findings of previous reviews that examined selected portions of this large body of evidence. We also discuss the implications of our findings for clinicians, investigators, and policy makers (e.g., professional societies that set guidelines on the use of contrast media, and health plans that make decisions about coverage for interventions).

N-Acetylcysteine Plus IV Saline Versus IV Saline With or Without Placebo

Our main meta-analyses indicated that compared with IV saline alone, low-dose N-acetylcysteine (1200 mg/daily or less) had a borderline clinically important decrease in CIN in patients receiving either intra-arterial or IV contrast media (risk ratio 0.75; 95 % CI: 0.63 to 0.89) or when either low (1200 mg daily or less) or high-dose (> 1200 mg daily) N-acetylcysteine was used in patients receiving LOCM (risk ratio 0.69; 95 % CI: 0.58 to 0.84). The strength of evidence was low for the first comparison (low-dose N-acetylcysteine) and moderate for the second comparison (in patients receiving LOCM), primarily due to limitations in the quality of studies and inconsistency in results. In comparison, a highly cited meta-analysis published by the Annals of Internal Medicine in 2008 reported a relative risk of 0.62 (95% CI 0.44 to 0.88) for preventing CIN when studies were combined irrespective of the dose of N-acetylcysteine.[215] An older meta-analysis, published in Lancet in 2003, reported a relative risk of 0.44 (95% CI 0.22 to 0.88) for preventing CIN with N-acetylcysteine.[216] In a recent meta-analysis published in PLoS One in 2013, the risk ratio for CIN with N-acetylcysteine was 0.68 (95% CI 0.46 to 1.02).[11] One study has questioned whether N-acetylcysteine is effective at preventing CIN or if it simply reduces serum creatinine.[216] This is an important finding; however, the reduction in serum creatinine reported as significant was measured at 4 hours, and it was insignificant at 48 hours, which was the timeframe for the assessment of CIN in this report.

Our review included many more studies than any of those reviews, and showed a much smaller effect for both high-dose and low-dose N-acetylcysteine. Our sensitivity analysis showed a clinically important benefit (greater than 25% relative risk reduction) with N-acetylcysteine plus IV saline compared with IV saline alone in reducing the incidence of CIN when LOCM was used, but not when IOCM was used. Although this difference could be due to methodological differences between the two sets of studies, the results were relatively consistent among the studies involving use of LOCM, while the 95% confidence interval of the aggregate risk ratio from studies involving use of IOCM ruled out a clinically important benefit. These findings raise the possibility that the effectiveness of N-acetylcysteine could vary by type of contrast media.

The risk of CIN generally is considered to be higher with intra-arterial than with IV administration of contrast media, raising the possibility that N-acetylcysteine could have greater benefit in patients receiving intra-arterial contrast media. When we stratified the analysis by route of administration of contrast media, the pooled risk ratios suggested the possibility of a difference in the effectiveness of N-acetylcysteine in the direction of having a greater effect with IV than intra-arterial contrast media: high-dose N-acetylcysteine (pooled risk ratio 0.78 versus

0.55, respectively for intra-arterial versus IV administration); low-dose N-acetylcysteine (pooled risk ratio 0.77 versus 0.62, respectively for intra-arterial versus IV administration). However, fewer studies have involved IV contrast media than intra-arterial contrast media, with resulting CIs that were much wider for studies involving IV contrast media than for studies involving intra-arterial contrast media. Thus, the evidence is insufficient to determine whether the effectiveness of N-acetylcysteine in preventing CIN differs according to whether IV versus intra-arterial administration was used. In contrast to a previous meta-analysis which reported a pooled relative risk of 0.20 (95% CI: 0.07 to 0.57) for preventing CIN in patients receiving IV contrast for a CT scan,[225] our analyses did not demonstrate a clear benefit of N-acetylcysteine for patients receiving IV contrast media. The previous meta-analysis included studies in which CIN was defined not only by change in serum creatinine but also by changes in cystatin C. In addition, in some of the studies included in this meta-analysis, the time frame for the definition of CIN was longer than 72 hours. These differences may explain why the previous analysis came to a different conclusions. More studies could help to determine whether there is a clinically important benefit of administering N-acetylcysteine to patients receiving an imaging test when the contrast media is administered IV.

Pre-test serum creatinine level may be an important covariate associated with CIN. Wu et al., 2013[225] found that the risk of CIN was reduced with N-acetylcysteine in patients with a baseline serum creatinine greater than 1.2 mg/d. They did not find a statistically significant benefit of N-acetylcysteine in patients with a baseline serum creatinine less than 1.2 mg/d. When we performed a sensitivity analysis similar to what Wu et al performed, we found that the mean baseline serum creatinine for each study was not associated with a difference in the effect of N-acetylcysteine on the incidence of CIN. This difference in results can be explained by somewhat different criteria for inclusion in the review, and our inclusion of studies that showed no benefit with N-acetylcysteine. Since it is plausible that pre-test serum creatinine level may be associated with an increased risk of CIN, further studies could help to elucidate whether N-acetylcysteine would be beneficial in patients with a high preexisting serum creatinine level.

Because of the great variability in study protocols as well as the conflicting results of the available clinical trials, the recommendations for N-acetylcysteine administration vary by organization. For example, the joint American College of Cardiology/American Heart Association 2012 guidelines do not recommend the use of N-acetylcysteine for patients receiving intra-arterial contrast in cardiac procedures.[226] In comparison, the 2012 Kidney Disease: Improving Global Outcomes *(KDIGO) Clinical Practice Guideline for Acute Kidney Injury* suggests using oral N-acetylcysteine with IV fluids in patients at increased risk for CIN, while acknowledging that the quality of evidence is very low.[226] The KDIGO recommendation is based on the argument that although the overall benefit for N-acetylcysteine is not consistent or overwhelming, it is inexpensive, appears to be safe, and has been shown in many studies to have an effect in reducing the risk of CIN.[21] Our analysis reveals a clinically important effect of low-dose N-acetylcysteine and is consistent with the KDIGO guidelines. Although N-acetylcysteine is inexpensive, and appears to be safe, the evidence may not be strong enough to support routine use, especially without stronger evidence on clinical outcomes other than the incidence of CIN.

Sodium Bicarbonate Versus IV Saline

Our meta-analysis demonstrated with low strength of evidence that IV sodium bicarbonate did not differ from IV saline in the incidence of CIN, although the confidence interval for the aggregate effect estimate was not precise enough to rule out the possibility of a clinically important benefit with sodium bicarbonate. The strength of evidence also was low that IV sodium bicarbonate did not produce a clinically important reduction in mortality or the need for renal replacement therapy when compared with IV saline. However, we found evidence for possible benefit of using sodium bicarbonate to prevent CIN in patients receiving LOCM although the observed difference was not statistically significant. Our main result is contrary to the conclusion of a recent meta-analysis of 19 clinical trials [107] investigating the effect of IV sodium bicarbonate. Our analysis included 19 RCTs which compared only IV sodium bicarbonate versus IV saline. In comparison, 5 of the 19 trials in the other meta-analysis were of combination regimens of IV sodium bicarbonate and N-acetylcysteine which may have biased the results in favor of sodium bicarbonate. This difference in the included studies may help to explain why we did not find a clinically important effect favoring IV sodium bicarbonate administration. Only two studies used IV contrast media administration, and hence it is difficult to draw a conclusion about the effect of bicarbonate administration on the prevention of CIN in patients receiving IV contrast media.[109,114]

N-Acetylcysteine Plus IV Saline Versus IV Sodium Bicarbonate

We found seven RCTs[36,46,56,58,70,74,132] and two observational studies[97,133] addressing the effects of N-acetylcysteine with concurrent administration of IV saline compared with IV sodium bicarbonate. However, the evidence was insufficient to support a conclusion about the comparative effectiveness of these two interventions in their ability to prevent CIN. We found no other meta-analyses on this head-to-head comparison. Limitations of the head-to-head comparison of N-acetylcysteine with concurrent administration of IV saline compared with IV sodium bicarbonate included the small number of studies, the varying regimens of fluid administration and N-acetylcysteine dosing, the variations in follow-up time, and variation in inclusion criteria which predispose to CIN, as we described in the results section. If additional studies are done to assess the comparative effectiveness of these two interventions, it would be important to focus on comparing IV sodium bicarbonate to N-acetylcysteine with IV saline especially in the setting of administration of LOCM, as both of these interventions demonstrated a clinically important benefit in this subgroup of patients. Again, it would be important to investigate this in patients with a high baseline serum creatinine in whom the risk of developing CIN is likely higher.

Statins

We found a clinically important protective effect against CIN when statins were administered in combination with IV fluids compared with IV fluids alone (8 RCTs), or in combination with N-acetylcysteine compared to N-acetylcysteine alone (5 RCTs), but the effect was only statistically significant in the latter comparison. We saw this treatment effect for both of the above comparisons in populations with chronic kidney disease,[137,141,142,144,145,153,154,156-158] diabetes mellitus[145,153,158] cardiac disease,[146,152,156] and in general populations.[141,155]

These results are consistent with five[227-231] out of six recent meta-analyses on the comparison of statins versus IV saline. The one recent meta-analysis that does not agree with the presence of a clinically important benefit included four studies and had a CI wide enough to not rule out a clinically important effect.[232] One of the meta-analyses showing significant decreases in CIN in the statin group did not show a decrease in CIN in patients with chronic kidney disease greater than stage 3.[228]

Currently, protocols for prevention of CIN in the United States do not include the use of statins. It may be time to reassess the role of statins in preventing CIN, especially since statins are readily available, easy to administer, and relatively inexpensive. Although our findings have moderate strength of evidence, there are also reasons to move forward cautiously. First, it is important to note that all studies evaluating the effect of statins to reduce the incidence of CIN were done using intra-arterial administration of contrast media. Hence, its protective effect against CIN for IV contrast media administration is not known. Second, it is possible that the findings reported in the studies of statins could be partly explained by a direct effect of statins on glomerular filtration rate that is independent of a protective effect on kidney function, as has been reported in one study.[233]

Adenosine Antagonists Plus IV Saline Versus IV Saline

Our analyses showed insufficient evidence to demonstrate an overall effect of theophylline or aminophylline plus IV saline when compared with IV saline alone for the prevention of CIN. There were wide variations in the effect estimates for individual studies, ranging from a ten-fold decrease in the risk of developing CIN with theophylline[168] to an almost 6-fold increase in the risk of developing CIN with theophylline.[167] Although our test of heterogeneity demonstrated that almost half of the uncertainty in the latter estimate could be explained by differences between studies, the p-value around this estimate was not statistically significant. Clinically, the variation could be explained by the heterogeneity of the populations in the studies, which ranged from patients with stable coronary artery disease[66] to those with moderate to severe chronic kidney disease.[31] A previous meta-analysis showed that the administration of theophylline or aminophylline was associated with less of a decline in kidney function than if it was not given.[234] However, IV saline was not administered in all the studies. In addition, the authors were unable to comment on the incidence of CIN based on the information provided in the articles. The authors of a meta-analysis looking at the effects of theophylline reported a trend toward a reduction in the incidence of CIN with theophylline use, but noted that the findings were inconsistent across studies.[235]

Overall, the evidence on the effects of adenosine antagonists on CIN was limited by medium study limitations based on the five criteria described in the methods for assessing risk of bias for individual studies, and considerable inconsistency and imprecision in the effect estimates. Only one of the relevant studies looked at IV contrast media administration; this may be relevant because the effect of prophylactic agents on CIN may differ depending on the route of contrast media administration, as mentioned previously.[6,236] The evidence also suffered from a lack of reporting on secondary outcomes such as need for dialysis, prolonged hospitalization, in-hospital mortality, and adverse drug effects. In this situation, the evidence seems insufficient to support much investment in further studies of the use of adenosine antagonists in preventing CIN.

Renal Replacement Therapy Versus IV Fluids

Hemodialysis and hemofiltration are invasive and expensive procedures that carry risks, but can remove some of the administered contrast. Our analyses did not demonstrate a decreased incidence of CIN in individuals receiving hemodialysis. However, limitations of the studies we found include small sample size, lack of rigorous controls, and uncertainties about the magnitude of delays between contrast administration and initiation of hemodialysis.

The studies comparing hemofiltration to IV saline reported that patients with severe chronic kidney disease have a lower risk for CIN with hemofiltration, especially when hemofiltration is started before the contrast media administration. These conclusions are limited by the fact that we only found two studies reporting this, and both were from the same authors and same institution. Another limitation is that the control groups received IV saline, while the patients undergoing hemofiltration received IV sodium bicarbonate as part of the procedure. Hemofiltration is expensive and requires patients to be admitted to and monitored in an intensive care unit. Furthermore, based on the design flaws in the reported trials and the paucity of studies examining this, further research is needed before proposing to expose patients to this invasive procedure as a prophylactic measure. It is important to note that the benefit of hemofiltration was only seen when it was initiated before the contrast media was given. Therefore, any added benefit may not be from removal of the contrast media, and it is proposed that the benefit may be secondary to the ability to provide more vigorous hydration. Clinical trials comparing hemofiltration with IV fluid protocols, and stronger trials that include investigation of the pharmacodynamics of the contrast media elimination during hemofiltration, may help better understand this procedure and its potential benefits.

Several additional limitations should be noted. Renal injury after contrast media administration occurs rapidly, and in these studies, hemodialysis may have been started too late to provide a significant benefit. Furthermore, the removal of creatinine by hemodialysis or hemofiltration limits the assessment of CIN as an outcome. While a false decrease in serum creatinine due to hemodialysis or hemofiltration is expected to bias the results toward a protective effect on the incidence of CIN, the results for hemodialysis actually suggested possible harm. The lack of a clinical benefit of renal replacement therapy may also be secondary to adverse events directly caused by the procedure (e.g., hypotension that may worsen kidney injury). Based on these results and the limitations and risks of the procedures, evidence is insufficient to support a clinically important benefit of renal replacement therapy.

Our findings coincide with the previously published systematic review by Cruz,[237] which concluded that renal replacement therapy does not provide any protection against CIN. That systematic review included additional studies that did not meet our inclusion criteria (a total of nine RCTs and two non-randomized RCTs).

Ascorbic Acid Versus IV Fluids

We found eight RCTs evaluating the use of ascorbic acid to prevent CIN. Our results showed a clinically important and statistically insignificant effect on CIN when administered in combination with IV fluids compared with IV fluids alone, and an unimportant effect when administered in combination with IV fluids and compared with N-acetylcysteine. We saw these results in populations with chronic kidney disease undergoing intra-arterial contrast media administration for coronary procedures. Overall, the strength of evidence was low for the finding that ascorbic acid given with IV fluids did not have a clinically important effect on preventing CIN when compared with IV fluids alone.

These results are consistent with but not as strong as those shown by a recent meta-analysis on the same comparison by Sadat el al.[181,227-232,238] Sadat el al. included data from nine RCTs comparing ascorbic acid with other treatments, and showed that patients receiving ascorbic acid had 33 percent less risk of CIN than those receiving other interventions. Our analysis included all of the five studies covered by Sadat et al. with the addition of one recent trial by Dvorsak et al.[183]

Sadat et al.'s results may differ in that they included in their review the results of three abstracts with positive results and another study that compared ascorbic acid versus N-acetylcysteine.[188]

Based on our review, the dose, timing and duration of ascorbic acid administration for prophylaxis against CIN did not affect the results. We also found that ascorbic acid did not have a clinically important benefit when compared with N-acetylcysteine.

Miscellaneous Comparisons

Many studies identified in our search did not fall into any of the main comparison groups listed above. For all of the miscellaneous comparisons, we were unable to support conclusions on the effectiveness of one intervention versus the other in preventing CIN.

Surprisingly little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving intra-vascular contrast media, despite the fact that current clinical practice often involves use of oral hydration alone. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if proven to be as effective as IV saline. Unfortunately, few studies investigated oral hydration versus IV saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus IV saline, especially for intra-arterial contrast procedures such as coronary angiography.

Overall Limitations

One of the biggest limitations of our systematic review is the marked heterogeneity of the study protocols, populations, definitions of CIN, and follow-up times in the studies. The heterogeneity limited our ability to assess all of the comparisons of interest. Because studies varied in their use and definition of kidney insufficiency as an inclusion criterion, and often did not report results stratified by baseline kidney function, it was very difficult to assess how the effectiveness of interventions might vary according to baseline kidney function. The studies generally did not report results in a manner that would permit assessment of how the effects of interventions might differ by other characteristics of patients. Also, some of the studies we found were excluded because their definition of CIN did not match our pre-specified definition; this is one of the reasons why our findings sometimes differed from those of other meta-analyses. We also found that studies examining the risk of CIN with different types of contrast media generally provided little detail about clinical indications for the diagnostic or therapeutic procedures, whether imaging was done on an urgent or elective basis or other details such as the severity of renal impairment.

A major limitation is that it is very difficult to apply the existing evidence to patients receiving IV contrast media because the vast majority of studies focused on patients receiving intra-arterial contrast media. It is possible that the risk of CIN is very low with the LOCM and IOCM protocols now used routinely with IV imaging. However, studies generally did not report results in a way that allows for determination of how the effects of interventions might differ by differences in the type, route, or volume of contrast media used.

Another limitation is that studies were very inconsistent in reporting on longer-term clinical outcomes that would be more important to patients than whether their serum creatinine level increased or their glomerular filtration rate decreased. In general, the evidence was insufficient to support conclusions about the comparative effects of interventions on long-term clinical outcomes.

The results of the review are susceptible to bias in the available evidence. Many of the included studies had important study limitations, including problems with selection bias (from inadequate methods for allocating patients to treatment assignments), detection bias (from limited blinding of outcome assessments), attrition bias (from incomplete outcome assessments), and reporting bias (from selective reporting of outcomes). In addition, publication bias is a concern in this body of literature, as reported by Vaitkus et al., 2007[239] who showed that the estimated effectiveness of N-acetylcysteine was greater in published articles than in unpublished abstracts. Despite our extensive search, we may have missed studies that have not been presented in a publicly available forum. Although we did not find evidence of asymmetry of results by study precision, statistical techniques have limited ability to detect publication bias. In general, we would expect the overall results of existing biases in this body of evidence to lead to an over-estimate of the effectiveness of interventions.

Although we included a broad search, our meta-analysis may overestimate the effect of prevention strategies to reduce CIN if studies with negative results were not reported in the sources we searched. The studies span over two decades and over time there may have been changes in the practice of CIN prevention such as increased screening, variation in definition of acute kidney injury, and variation in hydration. Such changes could contribute to observed differences in outcomes.

It is beyond the scope of this report to make a recommendation about screening for CIN. However, we acknowledge that CIN might be under-reported because patients often are discharged immediately after the imaging procedures are done.

Finally, this comprehensive review highlights the generally low strength of evidence on interventions for preventing CIN, while indicating that the greatest reduction in risk of CIN has been achieved with low-dose N-acetylcysteine in patients receiving LOCM, or with statins plus N-acetylcysteine.

Future Research

Populations

Future studies of the comparative effectiveness of interventions for preventing CIN should stratify patients according to their baseline risk of CIN, especially since it may be difficult to detect a difference in patients having a low risk of CIN. Patients with normal or near normal serum creatinine may have a lower risk for developing CIN compared to those with higher serum creatinine levels. Patients with risk factors for chronic kidney disease may have a higher risk of developing CIN than patients without such risk factors, The risk of CIN may be low enough in patients without diabetes mellitus or other risk factors, with the IV administration of LOCM and IOCM, to make it very difficult to demonstrate the effectiveness of an intervention for preventing CIN. To determine the effectiveness of interventions for preventing CIN in patients receiving IV contrast media, it may be necessary to perform large studies of patients having risk factors for developing chronic kidney disease.

Interventions

Since there was evidence for a clinically important benefit when N-acetylcysteine or sodium bicarbonate was given with LOCM, future studies could explore the effect by baseline risk of developing CIN in patients receiving LOCM.

The clinically important benefit of statins demonstrated in this analysis provides a rationale for further studies investigating whether the effect differs by statin dose, timing of administration, type of contrast media, or baseline risk of the patient population. Further investigation into the findings on statins versus IV saline could be performed through examination of the possible effect of risk modifiers such as baseline kidney function, concurrent use of nephrotoxic medications, and patient demographics. Future studies could explore the effect of statins on reducing CIN when contrast media is administered IV. In addition, studies could be done in individuals without cardiovascular risk factors to determine whether the effectiveness of statin therapy in reducing CIN occurs in the absence of the physiologic effects of statins on co-existing cardiovascular disease.

Little evidence exists on the comparative effectiveness of different regimens for giving fluids to patients receiving contrast media, despite the fact that current clinical practice often involves use of oral hydration alone for studies performed with IV contrast media administration. Oral hydration is a simple and potentially cost-effective strategy for preventing CIN, if shown to be as effective as IV saline. Unfortunately, very few studies investigated oral hydration versus IV saline. Hence, more studies are needed to investigate the effectiveness of oral hydration versus IV saline, especially for intra-arterial contrast procedures such as coronary angiography.

Outcomes

Regardless of which populations or interventions are involved, it is important that future studies use an accepted definition of CIN and report outcomes beyond CIN that are important to patients. Critical for future studies is more standardized reporting on adverse outcomes such as drug side-effects, need for hemodialysis, length of hospitalization, quality of life, and mortality.

Pathophysiology

The precise mechanism of CIN is not entirely understood. Some studies raise questions about the strength of the relationship between contrast administration and CIN. Thus, uncertainty persists about whether there is a direct causal relationship between administration of contrast media and the development of acute kidney injury. This area of research was beyond the scope of our review.[6,236,240] To develop more effective interventions for preventing CIN, it may be necessary to conduct additional research on the pathophysiological mechanisms by which contrast media may contribute to acute kidney injury. It would be important to differentiate the direct effects of contrast media from other factors that can contribute to acute kidney injury in patients receiving IV or intra-arterial contrast media.

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Appendix A. List of Acronyms

%	percent
ACE	angiotensin-converting-enzyme
ACS	acute coronary syndrome
ACT	Acetylcysteine for Contrat-Induced Nephropathy Trial
AHRQ	Agency for Healthcare Research and Quality
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALT	alanine aminotransferase
AMI	acute myocardial infarction
ARB	angiotensin II receptor blockers
CHF	congestive heart failure
CI	Confidence interval
CIN	Contrast induced nephropathy
CKD	Chronic Kidney disease
CM	Contrast media
Cr	Creatinine
CrCl	Creatinine clearance
CT	Computed tomography
eGFR	estimated glomerular filtration rate
EPC	Evidence-based practice center
ESRD	end stage renal disease
GFR	Glomular filtration rate
HD	hemodialysis
HF	hemofiltration
HOCM	high osmolar contrast media
ICU	intensive care unit
IOCM	Iso-osmolar contrast media
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KQ	Key Question
LOCM	Low-osmolar contrast media
LVEF	Left Ventricular Ejection Fraction
MACE	Major adverse cardiac events
MeSH	Medical subject heading
MI	myocardial infarction
NAC	n-acetylcyateine
NaCL	Sodium chloride
NaHCO3	Sodium bicarbonate
NR	Not reported
NS	Not significant
OR	odds ratio
PCI	percutaneous coronary intervention
PICOTS	Populations, interventions, comparators, outcomes, timing, setting
RCT	Randomized controlled trial
RIFLE	Risk, Injury, Failure, Loss of kidney function and End-Stage kidney disease
RR	Relative risk
RRT	Renal replacement therapy
SD	Standard deviation
SOE	Strength of evidence
SrCr	Serum creatinine
STEMI	ST Elevation Myocardial Infarction
T2DM	Type 2 diabetes mellitus
TOO	Task Order Officer

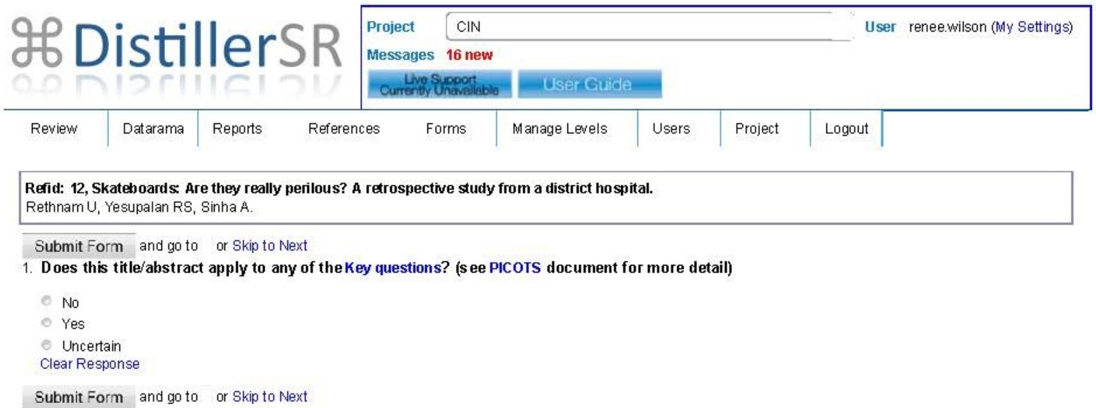
Appendix B. Detailed Search Strategy

Database	Search	Notes
PubMed	(("Kidney diseases"[mh] OR "Kidney disease"[tiab] OR "kidney diseases"[tiab] OR Nephropathy[tiab] OR "acute kidney injury"[mh] OR "acute kidney injury"[tiab] OR “acute renal injury”[tiab] OR "renal disease"[tiab] OR “renal diseases”[tiab]) AND ("contrast media"[mh] OR "contrast media"[tiab] OR "contrast medium"[tiab] OR "contrast material"[tiab])) NOT (animal[mh] NOT human[mh])	
Embase	('contrast medium'/exp OR 'contrast medium':ab,ti OR 'contrast media':ab,ti OR 'contrast material':ab,ti) AND ('kidney disease'/exp OR 'kidney disease':ab,ti OR 'kidney diseases':ab,ti OR nephropathy:ab,ti OR 'acute kidney injury':ab,ti OR 'renal disease':ab,ti OR 'acute renal failure':ab,ti OR 'acute renal injury':ab,ti)	12151 Limit to humans (study type): 9972 Limit to Article, Review, Conference Abstract, Conference Paper, Short Survey, Article in Press, Conference review (Publication type): 8952
Cochrane	ID Search #1 MeSH descriptor: [Kidney Diseases] explode all trees #2 "kidney disease":ti,ab,kw (Word variations have been searched) #3 nephropathy:ti,ab,kw (Word variations have been searched) #4 "acute kidney injury":ti,ab,kw (Word variations have been searched) #5 "renal disease":ti,ab,kw (Word variations have been searched) #6 "acute renal injury":ti,ab,kw #7 "renal diseases":ti,ab,kw #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Contrast Media] explode all trees #10 "contrast media":ti,ab,kw (Word variations have been searched) #11 "contrast material":ti,ab,kw (Word variations have been searched) #12 "contrast medium":ti,ab,kw #13 #9 or #10 or #11 or #12 #14 #8 and #13	Other reviews: 52 Trials: 368 Technology assessments: 4 Economic evaluations: 5

Appendix C. Screening and Data Abstraction Forms

Title

DistillerSR https://systematic-review.ca/Submit/RenderForm.php?id=1&hide_abstract=1



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Refid: 12, Skateboards: Are they really perilous? A retrospective study from a district hospital.
Rethnam U, Yesupalan RS, Sinha A.

Submit Form and go to or Skip to Next

1. **Does this title/abstract apply to any of the Key questions? (see PICOTS document for more detail)**

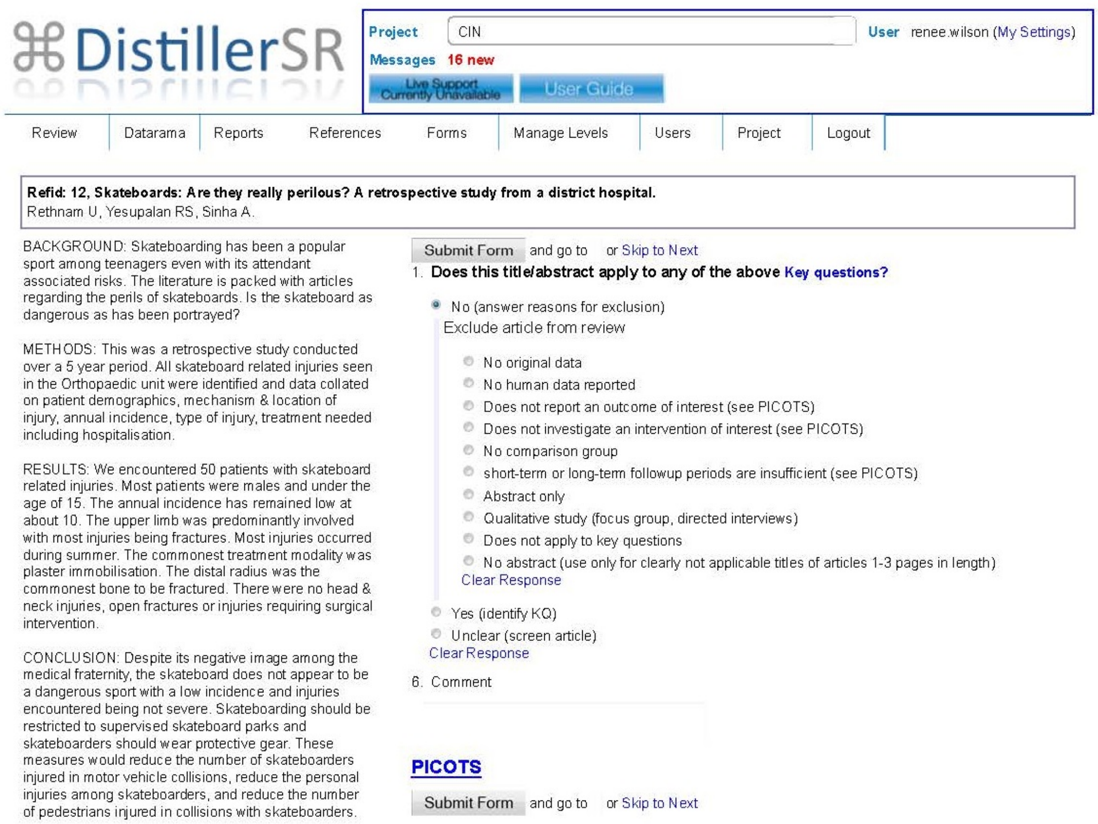
- No
- Yes
- Uncertain

Clear Response

Submit Form and go to or Skip to Next

Abstract Screening– NO

DistillerSR https://systematic-review.ca/Submit/RenderForm.php?id=4



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BACKGROUND: Skateboarding has been a popular sport among teenagers even with its attendant associated risks. The literature is packed with articles regarding the perils of skateboards. Is the skateboard as dangerous as has been portrayed?

METHODS: This was a retrospective study conducted over a 5 year period. All skateboard related injuries seen in the Orthopaedic unit were identified and data collated on patient demographics, mechanism & location of injury, annual incidence, type of injury, treatment needed including hospitalisation.

RESULTS: We encountered 50 patients with skateboard related injuries. Most patients were males and under the age of 15. The annual incidence has remained low at about 10. The upper limb was predominantly involved with most injuries being fractures. Most injuries occurred during summer. The commonest treatment modality was plaster immobilisation. The distal radius was the commonest bone to be fractured. There were no head & neck injuries, open fractures or injuries requiring surgical intervention.

CONCLUSION: Despite its negative image among the medical fraternity, the skateboard does not appear to be a dangerous sport with a low incidence and injuries encountered being not severe. Skateboarding should be restricted to supervised skateboard parks and skateboarders should wear protective gear. These measures would reduce the number of skateboarders injured in motor vehicle collisions, reduce the personal injuries among skateboarders, and reduce the number of pedestrians injured in collisions with skateboarders.

Submit Form and go to or Skip to Next

1. **Does this title/abstract apply to any of the above Key questions?**

- No (answer reasons for exclusion)
  Exclude article from review
  - No original data
  - No human data reported
  - Does not report an outcome of interest (see PICOTS)
  - Does not investigate an intervention of interest (see PICOTS)
  - No comparison group
  - short-term or long-term followup periods are insufficient (see PICOTS)
  - Abstract only
  - Qualitative study (focus group, directed interviews)
  - Does not apply to key questions
  - No abstract (use only for clearly not applicable titles of articles 1-3 pages in length)

  Clear Response
- Yes (identify KQ)
- Unclear (screen article)

Clear Response

6. Comment

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1. **Does this title/abstract apply to any of the above Key questions?**

- ○ No (answer reasons for exclusion)
- ● Yes (identify KQ)

  Include article for review

  - ☐ KQ1: IV contrast media (comparative effectiveness of interventions to prevent CIN)
  - ☐ KQ2: IA contrast media (comparative effectiveness of interventions to prevent CIN)
  - ☐ KQ3: IV contrast media--comparative benefits and harms of the media
  - ☐ KQ4: IA contrast media--comparative benefits and harms of the media
- ○ Unclear (screen article)

Clear Response

6. Comment

PICOTS

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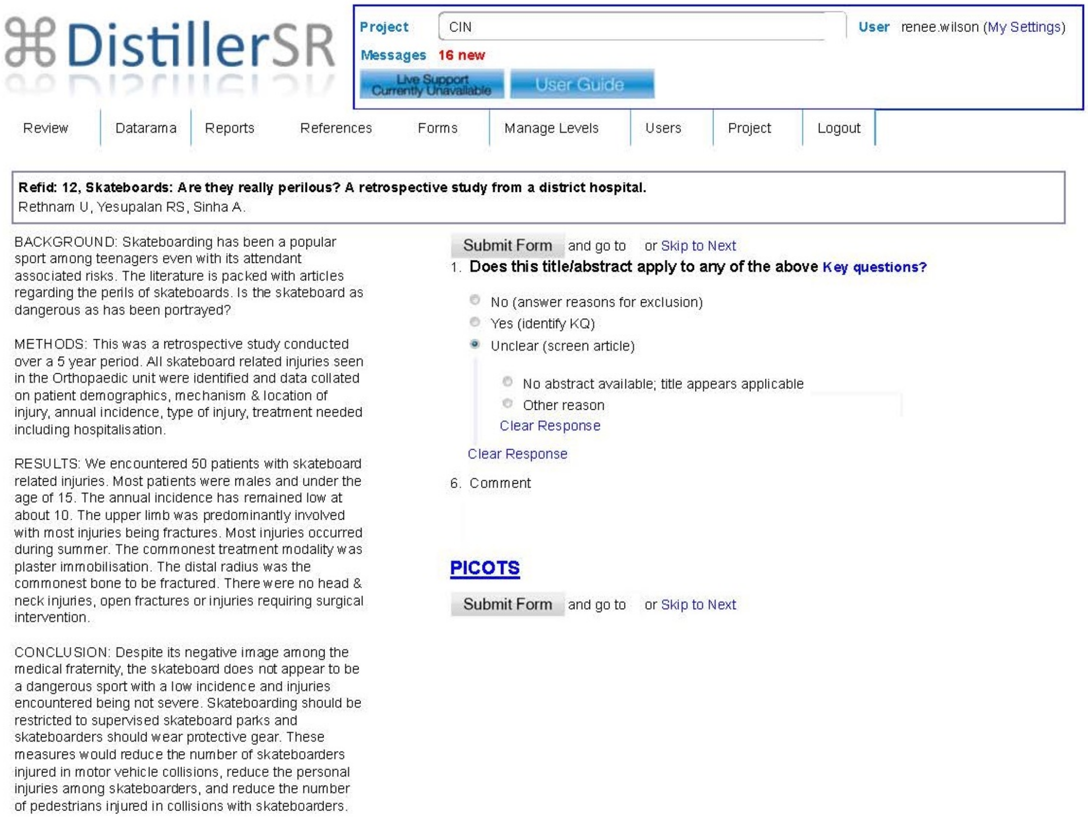
Abstract Screening– Unclear



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1. **Does this title/abstract apply to any of the above Key questions?**

- No (answer reasons for exclusion)
- Yes (identify KQ)
- Unclear (screen article)
  - No abstract available; title appears applicable
  - Other reason
  - Clear Response
- Clear Response

6. Comment

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1. **Does this ARTICLE apply to any of the above Key questions?**

- No (answer reasons for exclusion)

  Exclude article

  - No original data
  - No human data reported
  - Does not report an outcome of interest (see PICOTS)
  - Does not investigate an intervention of interest (see PICOTS)
  - No comparison group
  - study compared an intervention of interest to a comparator of interest, but the patient groups being compared were fundamentally different
  - short-term or long-term followup periods are insufficient (see PICOTS)
  - Abstract only
  - Qualitative study (focus group, directed interviews)
  - Does not apply to key questions
  - No abstract (use only for clearly not applicable titles of articles 1-3 pages in length)
  - Non-English language (identify language if possible)

  Clear Response

- Yes (identify KQ)
- Flag for discussion (**ONLY** use this option where queries can not be answerd by e-mail)

Clear Response

6. Comment

PICOTS

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Article Screening– YES

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1. **Does this ARTICLE apply to any of the above Key questions?**

- No (answer reasons for exclusion)
- Yes (identify KQ)

  Include article for data abstraction

  - KQ1: IV contrast media (comparative effectiveness of interventions to prevent CIN)
  - KQ2: IA contrast media (comparative effectiveness of interventions to prevent CIN)
  - KQ3: IV contrast media--comparative benefits and harms of the media
  - KQ4: IA contrast media--comparative benefits and harms of the media
- Flag for discussion (**ONLY** use this option where queries can not be answerd by e-mail)

Clear Response

6. Comment

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Participant Characteristics

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Participant Characteristics at Baseline

1. Does the study report baseline characteristics for subgroups seperately?
   (e.g., IV administration and IA administration)

   - Yes
   - No

   Clear Response

2. Identify group for baseline characteristics
   (You can submit this form multiple time)

   Select an Answer

Arm 1 (control/usual care)	Arm 2	Arm 3	Arm 4	Arm 5
3.	4.	5.	6.	7.

8. N at baseline

   - Total N
   - Arm 1 (control/usual care) n
   - Arm 2
   - Arm 3
   - Arm 4
   - Arm 5
   - Not reported

	Follow-up	Mean, median, max/min...	Units
9. Not reported Clear Response	10.	11. Select an Answer	12. Select an Answer

13. Sex

   - reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5

14. women, n women, %	15. women, n women, %	16. women, n women, %	17. women, n women, %	18. women, n women, %	19. women, n women, %

not reported

20. Age

reported

Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
21. mean Median Range	22. mean Median Range	23. mean Median Range	24. mean Median Range	25. mean median range	26. mean median range

not reported

27. Race/ethnicity

Reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
White, non-Hispanic	28. n %	29. n %	30. n %	31. n %	32. n %	33. n %
Black, non-Hispanic	34. n %	35. n %	36. n %	37. n %	38. n %	39. n %
Latino/Hispanic	40. n %	41. n %	42. n %	43. n %	44. n %	45. n %
Asian/Pacific Islander	46. n %	47. n %	48. n %	49. n %	50. n %	51. n %
American Indian/Alaska Native	52. n %	53. n %	54. n %	55. n %	56. n %	57. n %
58. Other	59. n %	60. n %	61. n %	62. n %	63. n %	64. n %

65. Other	66. n %	67. n %	68. n %	69. n %	70. n %	71. n %
72. Other	73. n %	74. n %	75. n %	76. n %	77. 2n %	78. 2n %

not reported

79. Education

Reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
< High School	80. n %	81. n %	82. n %	83. n %	84. n %	85. n %
Completed High School	86. n %	87. n %	88. n %	89. n %	90. n %	91. n %
College Degree	92. n %	93. n %	94. n %	95. n %	96. n %	97. n %
Post-graduate Degree	98. n %	99. n %	100. n %	101. n %	102. n %	103. n %
Years of education	104. mean median min max	105. mean median min max	106. mean median min max	107. mean median min max	108. mean median min max	109. mean median min max
110. Other	111. n %	112. n %	113. n %	114. n %	115. n %	116. n %
117. Other	118. n %	119. n %	120. n %	121. n %	122. n %	123. n %

124. Other	125. n %	126. n %	127. n %	128. n %	129. n %	130. n %

not reported

131. Smoking

reported

	Overall Group	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Current	132. n %	133. n %	134. n %	135. n %	136. n %	137. n %
Former	138. n %	139. n %	140. n %	141. n %	142. n %	143. n %
Ever	144. n %	145. n %	146. n %	147. n %	148. n %	149. n %
Never	150. n %	151. n %	152. n %	153. n %	154. n %	155. n %

not reported

156. Is the entire study population a subgroup (all particiupants have a specific disease or condition)?

Yes

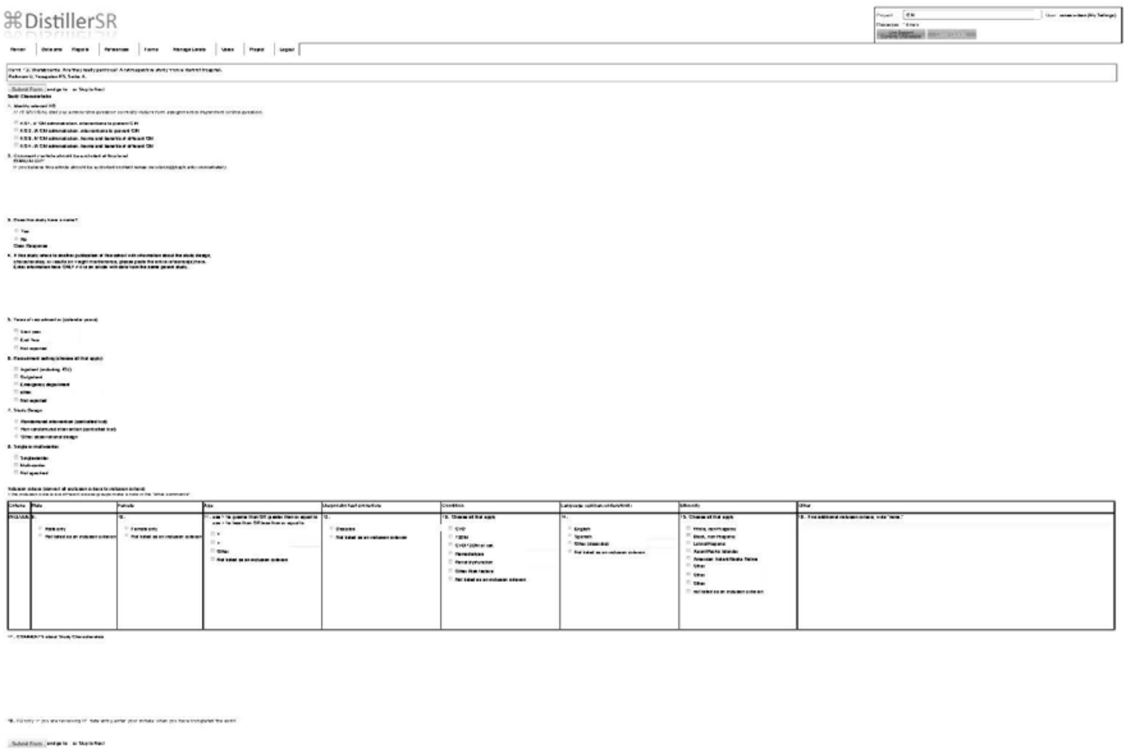
Condition	Define
Renal insufficiency (included CKD)	157.
Diabetes	158.
On Dialysis	159.
160. Other	161.
162. Other	163.

166. Other Comments

167. **R2 only: if you are reviewing R1 data entry, enter your initials when you have completed the audit**

Submit Form and go to or Skip to Next

Study Characteristics



Intervention KQ 1&2

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Intervention Description
Key Questions 1 and 2

The following questions are in place to identify the contrast media (CM) used in the study.
THIS IS NOT a KQ 1/2 study if:
The CM are being compared and no preventive measures are being used.

1. Does the study report Interventions for subgroups seperately?
(e.g., IV administration and IA administration)

- Yes
  2. Identify group for baseline characteristics
  (You can submit this form multiple time)

  Select an Answer
- No

Clear Response

3. Contrast Media used

- Iodixanol
- Iohexol
- Iomeprol
- Iopamidol
- Iopentol
- Iopromide
- Ioxaglate
- Ioxilan
- LOCM
- IOCM
- Not specified
- Other description

4. Contrast media administration route

- IV
- IA
- Not specified
- Other

Clear Response

5. Dose

- ☐ Define
- ☐ Not specified

6. Duration

- ○ Define
- ○ Not specified

Clear Response

7. Volume

- ○ Define
- ○ Not specified

Clear Response

The following questions are in place to idnetify and describe <u>preventive measures</u> for CIN.
Use Arm 1 EXCLUSIVELY for the control or standard care intervention. If there is not control, leave those columns blank under Arm 1
NOTE: the Arms below should match teh Arms described in the participant characteristics form.

	Arm 1 (control/usual care)	Arm 2	Arm 3	Arm 4	Arm 5
Administration route	8. ☐ **NO CONTROL OR USUAL CARE** ☐ Oral ☐ IV ☐ Not reported ☐ Other	9. ☐ Oral ☐ IV ☐ Not reported ☐ Other	10. ☐ Oral ☐ IV ☐ Not reported ☐ Other	11. ☐ Oral ☐ IV ☐ Not reported ☐ Other	12. ☐ Oral ☐ IV ☐ Not reported ☐ Other
Dose	13.	14.	15.	16.	17.
Duration	18.	19.	20.	21.	22.
Temporal association to CM administration	23. ☐ Prior to CM admin ☐ During CM admin ☐ After CM admin ☐ Not stated ☐ Other	24. ☐ Prior to CM admin ☐ During CM admin ☐ After CM admin ☐ Not stated ☐ Other	25. ☐ Prior to CM admin ☐ During CM admin ☐ After CM admin ☐ Not stated ☐ Other	26. ☐ Prior to CM admin ☐ During CM admin ☐ After CM admin ☐ Not stated ☐ Other	27. ☐ Prior to CM admin ☐ During CM admin ☐ After CM admin ☐ Not stated ☐ Other
Other details	28.	29.	30.	31.	32.

33. Comments

34. **R2 only: if you are reviewing R1 data entry, enter your initials when you have completed the audit**

Intervention KQ 3&4

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Intervention Description
Key Questions 3_4

The following questions are in place to idnetify and describe contrast media (CM)only.
Use Arm 1 EXCLUSIVELY for the control or standard care intervention. If there is no control, leave those columns blank under Arm 1
NOTE: the Arms below should match the Arms described in the participant characteristics form.

1. Does the study report Interventions for subgroups seperately?
(e.g., IV administration and IA administration)

- Yes
  2. Identify group for baseline characteristics
  (You can submit this form multiple time)
  Select an Answer
- No

Clear Response

	Arm 1 (control/usual care)	Arm 2	Arm 3	Arm 4	Arm 5
Contrast Medium (Media) used	3. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	4. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	5. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	6. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description	7. Iodixanol Iohexol Iomeprol Iopamidol Iopentol Iopromide Ioxaglate Ioxilan LOCM IOCM Not specified Other description
Administration route	8. **NO CONTROL OR USUAL CARE** IV IA Not reported Other	9. IV IA Not reported Other	10. IV IA Not reported Other	11. IV IA Not reported Other	12. IV IA Not reported Other

Clinical Outcomes Continuous

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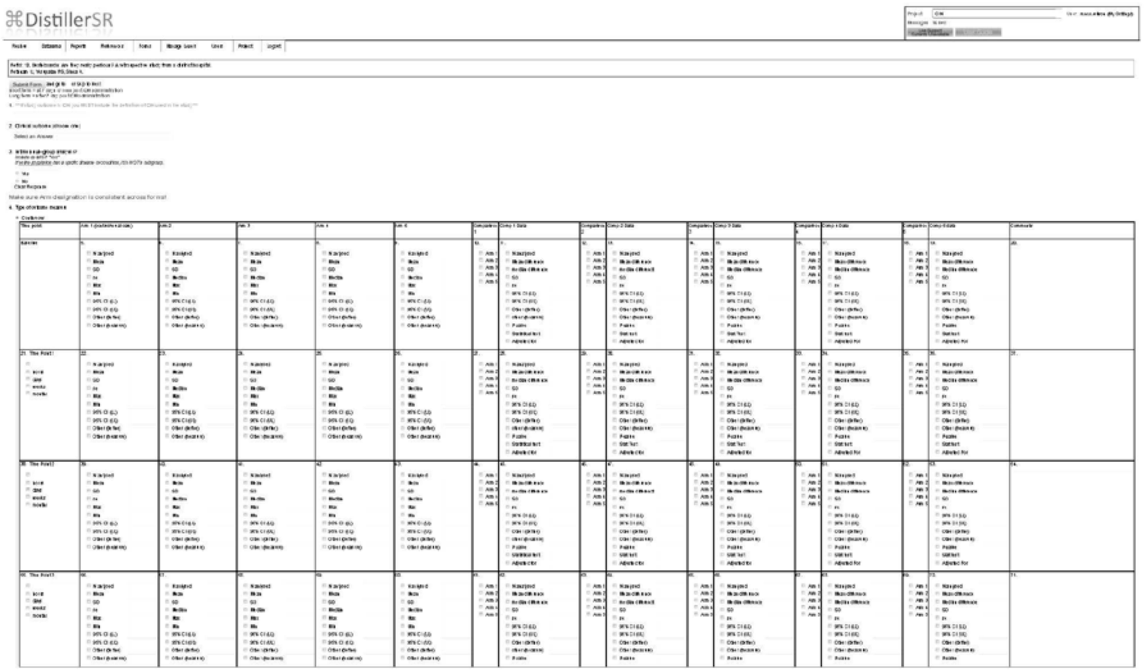

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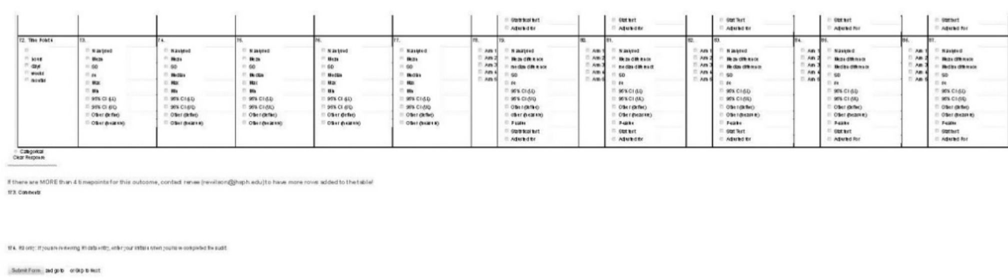

Clinical Outcomes Categorical

Adverse Events

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Adverse events

1. Did this study report adverse events?

Yes (inclueds a explicite report of no adverse events)

Harm	Describe
Imaging delay	2.
Need for additional imaging	3.
Fluid overload	4.
Heart failure	5.
Anaphalaxis	6.
7. Other	8.

Cochrane Risk of Bias

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Risk of Bias

1. Choose primary outcome (if study has more than 1 primary/main outcome, this form will need to be filled out multiple times).

Select an Answer

The full Cochrane Riskl of Bias tool can be accessed here: http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20assessment%20tool.pdf

Please refer to the link above while performing RoB assessments

Domain	Desription	Review Author's Judgement ...does the study:
Sequence Generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	2. Was the allocation sequence adequately generated? Select an Answer
Allocation Concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during enrollment.	3. Was allocation adequately concealed? Select an Answer
Blinding of Participants, Personnel, ad Outcome Assessors *Assessments should be made for each main outcome or class of*	Describe all measures used, if any to blind study personnel and participants from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	4. Was knowledge of the allocated intervention adequately prevented during the srudy? Select an Answer

outcomes		
Incomplete Outcome Data *Assessments should be made for each main outcome or class of outcomes*	Describe the completeness of outcome data for each main outcome, including attrition and exclusion from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compare with total randomized participants), reason for attrition/exclusions where reported, and any re-inclusions in analyses performed by teh review authors.	5. Were incomplete oucome data adequately addressed? Select an Answer
Selective Outcome Reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	6. Are reports of the study free of suggestion of selective outcome reporting? Select an Answer
Other Sources of Bias	State any important concerns about bias not addresses in the other domains in the tool.	7. Was the study apparently free of other problems that could put it at a high risk of biase? Select an Answer

8. Comments

9. R2 only: If you are reviewing R1 data entry, enter your initials when you have completed the audit

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Appendix D. List of Excluded Studies

Exclusion: Abstract Only.

M. R. Gandhi, P. Brown, C. A. Romanowski, S. K. Morcos, S. Campbell, A. M. el Nahas and T. A. Gray. The use of theophylline, an adenosine antagonist in the prevention of contrast media induced nephrotoxicity. Br J Radiol. 1992. 65:838

M. S. Davenport, S. Khalatbari, N. R. Dunnick, J. R. Dillman and J. H. Ellis. Contrast-induced nephrotoxicity: Risk of intravenous low osmolality iodinated contrast material stratified by estimated glomerular filtration rate. Abdominal Imaging. 2013. 38:628

J. Sugioka, M. Inagaki, S. Fukuzawa, A. Ikeda, S. Okino, J. Maekawa, S. Maekawa, S. Ichikawa, N. Kuroiwa and S. Okamoto. Risk prediction of contrast-induced nephropathy in diabetic patients undergoing primary percutaneous coronary intervention for acute myocardial infarction. Cardiology (Switzerland). 2013. 125:164

M. Fujimoto, K. Waseda, H. Takashima, K. Maeda, K. Asai, Y. Kuroda, T. Kosaka, A. Kurita, Y. Kuhara, H. Ando, S. Sakurai, D. Kato, A. Suzuki, Y. Nakano, T. Niwa, K. Mukai, S. Sato, T. Mizuno and T. Amano. Effect of oral hydration on renal function after coronary catheterization. American Journal of Cardiology. 2013. 111:89B

M. Habib, A. Hillis and A. Hamad. The role of ascorbic acid or n-acetylcysteine or combination in prevention of contrast-induced nephropathy in high-risk patients with ischemic heart disease. International Journal of Cardiology. 2013. 163:S64

M. Habib, A. Hillis and A. Hamad. Low dose of N-acetylcysteine plus ascorbic acid versus hydration with (saline 0.9%) for prevention of contrast-induced nephropathy in patients undergoing coronary angiography. International Journal of Cardiology. 2013. 163:S81

S. Hamdi, W. Selmi, A. Hraiech, W. Jomaa, K. B. Hamda and F. Maatouk. Prevention of contrast induced nephropathy in patients undergoing coronarography with ascorbic acid. JACC: Cardiovascular Interventions. 2013. 6:S22

J. Samide, N. Saad, T. Abraham and E. Balmir. A retrospective evaluation on the usage of iodinated contrast media in an Urban hospital setting. Critical Care Medicine. 2012. 40:265

J. Kooiman, Y. W. Sijpkens, H. C. Brulez, J. P. P. De Vries, J. F. Hamming, A. J. Van Der Molen, N. J. Aarts, S. C. Cannegieter, T. J. Rabelink and M. V. Huisman. Randomized study of short prehydration with sodium bicarbonate versus standard pre- and posthydration with sodium chloride to prevent contrast induced acute kidney injury: The Salina trial. Circulation. 2012. 126:#pages#

A. M. Fayed. Human albumin versus isotonic sodium bicarbonate in prevention of contrast induced nephropathy in critically ill patients. Intensive Care Medicine. 2012. 38:S243-S244

X. Qun and L. Shijuan. Protection of n-acetylcysteine for patients with contrast induced nephropathy after percutaneous coronary intervention treatment. Heart. 2012. 98:E214

R. Li and H. Chen. Prevention of contrast-induced nephropathy with ascorbic acid. Heart. 2012. 98:E211

J. Juch, J. Le Noble and N. Foudraine. Incidence and prevention of contrast induced nephropathy (CIN) in the ICU: Preventive administration of Na+ bicarbonate is not effective. Single dose amino-glycoside is a major risk factor. Intensive Care Medicine. 2012. 38:S46

G. Deray, L. Marti-Bonmati, O. Rouviere, L. Bacigalupo, B. Maes, T. Hannedouche, F. Vrtovsnik, C. Rigothier, J. Billiouw and P. Campioni. Renal safety evaluation after Gd-DOTA-enhanced-MRI compared with non-enhanced-MRI in patients at high risk of developing contrast medium induced nephropathy. Journal of Medical Imaging and Radiation Oncology. 2012. 56:90

M. Erturk, E. Akbay, G. Kurtulus, N. Isiksacan, M. Gul, I. F. Akturk, O. Surgit, F. Uzun, A. Yildirim and N. Uslu. Effect of iv or oral N-acetylcysteine in the prevention of contrast-induced nephropathy in patients with moderate to severe renal insufficiency. European Heart Journal. 2012. 33:77

A. K. Singh and J. A. Kari. 24-hour isotonic sodium choloride was better than 7-hour sodium bicarbonate for preventing CIN. Annals of Internal Medicine. 2012. 157:JC1-9

V. Brulotte, F. A. Leblond, S. Elkouri, E. Therasse, V. Pichette and P. Beaulieu. Impact of sodium bicarbonate administration and N-acetylcysteine on the prevention of contrast media-induced nephropathy in endovascular aortic aneurysm repair. European Journal of Anaesthesiology. 2012. 29:66

G. Gu, R. Lu, W. Cui, F. Liu, Y. Zhang and X. Yang. Low-dose furosemide administered with adequate hydration prevents contrast-induced

nephropathy in patients undergoing coronary angiography. Circulation. 2012. 125:e868
K. Chatani, M. Abdel-Wahab, R. Toelg, V. Geist, M. Marwan, A. E. Mostafa and G. Richardt. Impact of iso-osmolar versus low-osmolar contrast agents on contrast-induced acute kidney injury in unselected patients undergoing TAVI. EuroIntervention. 2012. 8:N160
A. Lacquaniti, V. Donato, M. Rosaria Fazio, S. Lucisano, V. Cernaro, R. Lupica and M. Buemi. Contrast media, nephrotoxicity and neutrophil-gelatinase associated lipocalin: Between doubts and certainties. Nephrology Dialysis Transplantation. 2012. 27:ii354-ii355
S. Traub, A. Mitchell, A. E. Jones, A. Tang, J. O'Connor, J. Kellum and N. Shapiro. A randomized trial of N-acetyl cysteine and saline versus normal saline alone to prevent contrast nephropathy in emergency department patients undergoing contrast enhanced computed tomography. Academic Emergency Medicine. 2012. 19:S22
B. C. Chua, A. S. Aprjanto, N. Hamada and S. Sultan. Contrast Induced Nephropathy and Chronic Kidney Disease (CIN/CKD) as a consequence of utilising non ionic Iso-Osmolar Contrast Media (IOCM) versus Low- Osmolar Contrast Media (LOCM) following lower extremity endovascular revascularisation (EvR): A 5 years parallel group observational study. Irish Journal of Medical Science. 2012. 181:S16-S17
S. Ebisawa, T. Saigusa, K. Odagiri, S. Aso, K. Aizawa, M. Koshikawa, H. Kasai, A. Izawa, T. Tomita, Y. Miyashita, S. Kumazaki, T. Yaguchi, H. Hioki, J. Koyama, U. Ikeda, T. Kurita, M. Kimura and T. Suzuki. Impact of minimum contrast media on percutaneous coronary intervention for preventing contrast induced nephropathy in patients with coronary artery disease. Circulation. 2011. 124:#pages#
N. Mayaud, K. Isaaz, C. Mariat, A. Cerisier, M. Lamaud, L. Richard and A. Da. Contrast induced nephropathy in patients with normal renal function undergoing complex PCI with high dose of contrast media: Predictive value of Cystatin C. Journal of the American College of Cardiology. 2011. 58:B138
M. Elshawadfy, M. A. Oraby, H. M. Ismail and F. A. Maklady. Effectiveness of theophylline in prevention of contrast-induced nephropathy in risky Egyptian patients undergoing elective coronary angiography or percutaneous intervention: A randomized controlled trial. Journal of the American College of Cardiology. 2011. 58:B136
M. Menozzi, P. Magnavacchi, E. Puggioni, M. Valgimigli, L. Vignali, V. Guiducci, G. Pignatelli, P. Giacometti and A. Manari. Contrast induced acute kidney injury in patients undergoing primary angioplasty for acute myocardial infarction. a randomized trial on hydration with saline or bicarbonate. Journal of the American College of Cardiology. 2011. 58:B137-B138
A. Momeni, A. Ebrahimi and A. Khaledi. Comparison of three methods of contrast nephropathy prophylaxis in azotemic patients. Iranian Journal of Kidney Diseases. 2011. 5:10
S. Bajaj, M. Sharma, R. Parikh, S. Patel, N. Gupta, C. Chandran, A. Hamdan, F. Shamoon and M. Bikkina. Contrast induced nephropathy in patients with chronic kidney disease undergoing coronary angiography. Chest. 2011. 140:#pages#
W. Li, D. Li, T. Xu, Y. Zhang, H. Zhu and F. Han. Prevention of contrast-induced acute kidney injury with ascorbic acid and prostaglandin e1 in high risk factors patients undergoing PCI. Heart. 2011. 97:A151
Y. Miao and Z. Yu-Jie. Efficacy of short-term high-dose atorvastatin for prevention of contrastinduced nephropathy in patients with st segment elevation myocardial infarction undergoing percutaneous coronary intervention. Heart. 2011. 97:A229
X. Hou, Y. J. Wang, Q. X. Yin, J. L. Miao and H. Jiang. Prevention of contrast-induced nephropathy comparison of two hydration regimens in elderly patients undergoing percutaneous coronary intervention. Heart. 2011. 97:A230
L. Bertelli, F. A. Sgura, M. Manicardi, A. Campioli, G. Spadafora, C. Leuzzi, R. Rossi, G. Biondi Zoccai, G. M. Sangiorgi and M. G. Modena. Mid-term outcomes of iodixanol versus iomeprol contrast medium after primary angioplasty for st elevation myocardial infarction. European Heart Journal. 2011. 32:881
M. Brueck, H. Cengiz and A. Boening. Comparison of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced nephropathy in patients with renal insufficiency undergoing elective cardiac catheterization. European Heart Journal. 2011. 32:261-262
M. Mockel, M. J. Dumichen, K. Friedrich, Y. Kuhnle, J. O. Vollert, J. Searle, V. Combe, C. Schwenke and M. Schroder. Invasive renal hemodynamics after left ventricular and coronary angiography with randomised use of different contrast media. EuroIntervention. 2011. 7:M15
X. Li, Y. Wang, N. Fu, R. Zhao, J. Xiao, Z. Li and H. Cong. Atorvastatin combining probucol can

reduce the renal impairment induced with contrast-medium. EuroIntervention. 2011. 7:M17

Y. Chen, S. Hu, Y. Liu, L. Wang, G. Fu and Q. He. A randomised, double-blinded comparison of Iopromide and Iodixanol in renally impaired patients undergoing cardiac catheterisation (DIRECT study). EuroIntervention. 2011. 7:M11

J. Min, A. Ryan and J. Spalding. Renal morbidity, mortality, and costs in individuals undergoing invasive cardiac catheterization procedures with low-osmolar contrast media: A large retrospective database analysis. Value in Health. 2010. 13:A351

Y. Han, S. Wang, X. Wang, F. Li, X. Zhao and Q. Jing. Contrast-induced nephropathy following coronary intervention in elderly, renally impaired patients: A randomised comparison of the renal safety of iodixanol and iopromide. EuroIntervention. 2010. 6:#pages#

S. Rastelli, L. Zanoli, C. Marcantoni, J. Blanco, C. Tamburino and P. Castellino. Contrast media related risk of contrast induced nephropathy. NDT Plus. 2010. 3:iii56

H. El-Fishawy, N. Shaheen and A. Soliman. Ascorbic acid and acetylcysteine for prevention of acute deterioration of renal function following elective aorto-iliac and coronary angioplasty. NDT Plus. 2010. 3:iii300

S. S. Brar, A.-J. Shen, M. B. Jorgensen, V. J. Aharonian, V. Koshkaryan and A. I. Shah. A randomized controlled trial for the prevention of contrast induced nephropathy with sodium bicarbonate vs. sodium chloride in patients undergoing coronary angiography: 2-year results from the MEENA Trial. #journal#. 2010. #volume#:B77

J. G. Lavenberg and C. A. Umscheid. Prevention of contrast-induced nephropathy: acetylcysteine, sodium bicarbonate, or saline (Structured abstract). #journal#. 2011. #volume#:#pages#

Exclusion: Followup less than one year

E. A. McGillicuddy, K. M. Schuster, L. J. Kaplan, A. A. Maung, F. Y. Lui, L. L. Maerz, D. C. Johnson and K. A. Davis. Contrast-induced nephropathy in elderly trauma patients. J Trauma. 2010. 68:294-7

T. Nozue, I. Michishita, T. Iwaki, I. Mizuguchi and M. Miura. Contrast medium volume to estimated glomerular filtration rate ratio as a predictor of contrast-induced nephropathy developing after elective percutaneous coronary intervention. J Cardiol. 2009. 54:214-20

S. Khanal, N. Attallah, D. E. Smith, E. Kline-Rogers, D. Share, M. J. O'Donnell and M. Moscucci. Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. Am J Med. 2005. 118:843-9

Exclusion: Unobtainable

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Exclusion: No comparison group of interest

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Exclusion: Qualitative study

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Exclusion: Study compared an intervention of interest to a comparator of interest, but the patient groups being compared were fundamentally different

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Appendix E. Evidence Tables for Main Comparisons

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Abaci, 2015[1]	CKD	Total		208	48-72 hours					
		1	IV normal saline	105		24 (26.6)	67.7 (8.9)	NR	NR	NR
		2	IV normail saline +risovustatin	103		34 (36)	67.5 (8.9)	NR	NR	NR
Acikel, 2010[2]	LDL cholesterol >70 mg/dl	Total		240	48 hrs	88 (37)	59.8	NR	NR	94 (39.2)
		1	IV Normal Saline	80		29 (36.2)	60.8	NR	NR	30 (37.5)
		2	IV Normal Saline + Oral Atorvastatin	80		29 (36.2)	58.7	NR	NR	32 (40.0)
		3	IV Normal Saline + Chronic Statin Therapy (non-randomized group)	80		30 (37.5)	59.8	NR	NR	32 (40.0)
ACT, 2011[3]	Cr < 176 umol/L	Total		2308	30 Days	NR	NR	NR	NR	NR
		1	Placebo	1136		447(39.3)	68.1	NR	NR	NR
		2	Oral NAC	1172		445(38)	68	NR	NR	NR
Albabtain, 2013[4]	SrCr ≥1.3 mg/dl or on diabetes medication	Total		243	4-5 days	66 (27)	61	NR	NR	NR
		1	IV Normal Saline	66		12 (18.2)	60	NR	NR	NR
		2	Oral Ascorbic Acid + IV Normal Saline	57		19 (33.3)	59	NR	NR	NR
		3	Oral NAC + IV Normal Saline	62		18 (29.0)	62	NR	NR	NR
		4	Oral NAC + Oral Ascorbic Acid + IV Normal Saline	58		17 (29.3)	64	NR	NR	NR
Alexopoulos, 2010[5]	SrCr ≥1.2 mg/dL (106umol/L)	Total		222	2-5 days	17 (7.7)	65	NR	NR	NR
		1	IV Normal Saline + Oral Placebo	109		NR	NR	NR	NR	NR
		2	IV Normal Saline + Oral Ascorbic Acid	113		NR	NR	NR	NR	NR
Alioglu, 2013[6]	General	Total		113	NR	NR	NR	NR	NR	NR
		1	Control	49		(34.4)	60.84	NR	NR	NR
		2	NAC	64		(32.7)	62.73	NR	NR	NR
Allaqaband, 2002[7]	General	Total		123	48 hrs	52(42)	71	NR	NR	NR
		1	0.45% Saline	40		16(67)	71	NR	NR	NR
		2	0.45% Saline + NAC	45		17(38)	70	NR	NR	NR
		3	0.45% Saline + Fenoldopam	38		19(50)	71	NR	NR	NR
Amini, 2009[8]	Chronic kidney disease, defined as SrCr concentration ≥ 1.5 mg/dL for men and ≥ 1.4 mg/dL for women	Total		90	48 hrs	NR	NR	NR	NR	NR
		1	Placebo	45		11(24)	65.09	NR	NR	NR
		2	N-Acetylcysteine	45		25(56)	63.25	NR	NR	NR

Evidence Table 1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Aslanger, 2012[9]	STEMI, ST-segment elevation myocardial infarction,	Total		312	72 hrs	NR	NR	NR	NR	NR
		1	Placebo	99		23(26)	57.2	NR	NR	NR
		2	IV NAC	108		22(20)	56.1	NR	NR	NR
		3	Intra-renal NAC	105		23(22)	55.9	NR	NR	NR
Awal, 2011[10]	SrCr ≥ 1.2mg/dl	Total		100	24 hrs	NR	NR	NR	NR	NR
		1	IVF Normal saline	50		10(20)	52;Range: 32-80	NR	NR	NR
		2	IVF Normal saline+N acetylcysteine	50		8(16)	58;Range: 38-76	NR	NR	NR
Azmus, 2005[11]	General	Total		397	48 hrs	NR	NR	NR	NR	NR
		1	Placebo	201		84(41.8)	67	NR	NR	NR
		2	NAC	196		79(40.3)	66	NR	NR	NR
Baker, 2003[12]	General	Total		80	Mean 96 hrs	10	NR	NR	NR	NR
		1	Saline only	39		6	67.4	NR	NR	NR
		2	IV saline + NAC	41		4	67.4	NR		NR
Baskurt, 2009[13]	Moderate degree chronic kidney disease with eGFR between 30 and 60 mL min1.73 m2	Total		217	12 Months	87	67.4	NR	NR	NR
		1	Hydration	72		31	67.1	NR	NR	NR
		2	Hydration + N-acetylcysteine	73		27	67.9	NR	NR	NR
		3	Hydration + N-acetylcysteine + theophylline	72		29	67.1	NR	NR	NR
Baranska-Kosakowska, 2007[14]	Heart transplant patients	Total		112	NR	11 (9.8)	NR	NR	NR	NR
		1	IV Normal Saline	57		6 (11)	52	NR	NR	NR
		2	IV NAC + IV Normal Saline	55		5 (9)	55	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Beyazal, 2014[15]	serum creatinine values between 1.1 and 3.1 mg/dL	Total		60	7 Months	27(45)	62.7; Range: 29-80	NR	NR	Current: 30(50)
		1	IV 0.9% Normal Saline	20		7(35)	NR	NR	NR	Current: 12(60)
		2	IV NaHCO3 + 5% dextrose	20		11(55)	NR	NR	NR	Current:9(45)
		3	IV 0.9% Normal Saline + Diltiazem	20		9(45)	NR	NR	NR	Current:9(45)
Bilasy, 2012[16]	Moderate risk for CIN, moderate risk for CIN as defined by Mehran risk score	Total		60	72 hrs	NR	NR	NR	NR	NR
		1	IVF NaCl	30		15(50)	57.23	NR	NR	NR
		2	Theophylline	30		9(30)	56.8	NR	NR	NR
Boccalandro, 2003[17]	General	Total		179	48 hrs	NR	NR	NR	NR	NR
		1	No acetylcysteine + hydratrion	106		47	66	NR	NR	NR
		2	Acetylcysteine + hydration	73		24	66	NR	NR	NR
Boscheri, 2007[18]	Chronic renal failure and stable SrCr >120 umol/l	Total		143	6 days	40 (28)	NR	NR	NR	NR
		1	Placebo + IV Normal Saline	69		20 (29)	71	NR	NR	NR
		2	Oral Ascorbic Acid + IV Normal Saline	74		20 (27)	71	NR	NR	NR
Boucek, 2013[19]	Presence of diabetes upon enrollment, SrCr > 100 umol/L (>1.136 mg/dl)	Total		120	2 Days	NR	NR	NR	NR	NR
		1	NaCl	59		15(34.1)	67	NR	NR	NR
		2	NaHCO3	61		15(32.6)	63	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Brar, 2008[20]	Stable renal disease(not defined)	Total		323	6 Months	NR	NR	NR	NR	NR
		1	NaCl	165		62 (35.2)	Median, 71 ; Range, 65-76	NR	NR	NR
		2	NaHCO3	158		66 (37.7)	Median, 71 ; Range, 65-75	NR	NR	NR
Briguori, 2002[21]	Cr >1.2mg/dl, creatinine clearance <70ml/min	Total		183	5 Days	NR	NR	NR	NR	NR
		1	Control	91		10(11)	64+/-9	NR	NR	NR
		2	NAC	92		15(16)	64+/-9	NR	NR	NR
Briguori, 2007[22]	CKD with stable Cr at 2.0 mg/dL and/or estimated glomerular filtration rate 40	Total		326	7 days	NR	NR	NR	NR	NR
		1	IV Normal Saline + oral NAC	111		21 (19)	71	NR	NR	NR
		2	IV NaHCO3 + oral NAC	108		13 (12)	70	NR	NR	NR
		3	IV Normal Saline + IV ascorbic acid + oral NAC	107		27 (21.5)	69	NR	NR	NR
Brueck, 2013[23]	SrCr ≥1.3 mg/dl	Total		499	72 hours	NR	NR	NR	NR	NR
		1	Placebo + IV Normal Saline	198		75(37.9)	74	NR	NR	NR
		2	NAC + IV Normal Saline	199		69(34.7)	75	NR	NR	NR
		3	Ascorbic Acid + IV Normal Saline	102		37(36.3)	75	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Burns, 2010[24]	General	Total		42	5 Days	NR	NR	NR	NR	NR
		1	Placebo	21		NR	NR	NR	NR	NR
		2	NAC	21		NR	NR	NR	NR	NR
Buyukhatipoglu, 2010[25]	Coronary artery disease	Total		60	24 hours	18 (30)	NR	NR	NR	NR
		1	IV Normal Saline	30		9 (30)	61.8	NR	NR	NR
		2	IV NAC + IV Normal Saline	30		9 (30)	58.9	NR	NR	NR
Carbonell, 2007[26]	General	Total		216	48 Hours	NR	NR	NR	NR	NR
		1	Placebo	109		30(27.5)	63.1+/-13.7	NR	NR	NR
		2	NAC	107		21(18.6)	63.1+/-13.7	NR	NR	NR
Carbonell, 2010[27]	SrCr >1.4	Total		0	2 Days		NR	NR	NR	NR
		1	Placebo	42		8(19)	NR	NR	NR	Current: 19(43)
		2	NAC	39		8(20)	NR	NR	NR	Current: 24(61)
Castini, 2010[28]	General	Total		156	5 Days	NR	NR	NR	NR	NR
		1	IV normal saline	51		8 (16)	72.7+/-8.2	NR	NR	NR
		2	Oral NAC + IV normal saline	53		3 (6)	70.5+/-7.2	NR	NR	NR
		3	IV NaHCO3 in 5% dextrose in water	52		8 (15)	70.0+/-83.	NR	NR	NR
Chousterman, 2011[29]	General	Total		116	72 hrs	NR	NR	NR	NR	NR
		1	Usual care, No NAC	54		NR	65 (50-72)	NR	NR	NR
		2	NAC	62		NR	63 (47-73)	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Chousterman, 2013[30]	ICU patients	Total		140	72 hrs	NR	NR	NR	NR	NR
		1	Saline	70		NR	Median: 63; Range: 47-73	NR	NR	NR
		2	NAC	70		NR	Median: 65;Range: 50-72	NR	NR	NR
Demir, 2008[31]	General	Total		97	3 Days	43(44)	NR	NR	NR	NR
		1	Saline	20		5(25)	58+/-11.3	NR	NR	NR
		2	Saline + NAC (NAC)	20		9(45)	62.0+/-15.8	NR	NR	NR
		3	Saline + Misopriatol (M)	20		11(55)	56.5+/-13.0	NR	NR	NR
		4	Saline + Theophylline (T)	20		9(45)	56.3+/-13.0	NR	NR	NR
		5	Saline + Nifedipine(N)	17		9(53)	60.1+/-10.7	NR	NR	NR
Durham, 2002[32]	Baseline SrCr >1.7 mg/dL.	Total		79	144 hrs	NR	NR	Reported	NR	NR
		1	IV hydration plus placebo	41		13	69.8	White: 36 Black: 2 Latino: 3 Other: 0	NR	NR
		2	IV hydration plus NAC	38		14	71.4	White: 32 Black: 4 Latino: 1 Other: 1	NR	NR
Dvorsak, 2013[33]	Stable serum creatinine >107 umol/L	Total		81	4 Days	22 (27)	71	NR	NR	NR
		1	IV Normal Saline + placebo	41		13 (32)	71	NR	NR	NR
		2	IV Normal Saline + ascorbic acid	40		9 (22)	71	NR	NR	NR
Erturk, 2014[34]	Moderate to severe renal dysfunction	Total		307	1 year	112 (36.5)	66	NR	NR	Current: 140 (45.6)
		1	IV normal saline	103		38 (36.9)	67	NR	NR	Current: 51 (49.5)
		2	Oral NAC + IV normal saline	102		38 (37.2)	65	NR	NR	Current: 48 (47.1)
		3	IV NAC + IV normal saline	102		36 (35.3)	66	NR	NR	Current: (41 (40.2)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Ferrario, 2009[35]	Moderate to severe chronic renal failure: <55ml/min creatinine clearance	Total		200	3 Days	NR	NR	NR	NR	NR
		1	Placebo	101		38(38)	75	NR	NR	NR
		2	NAC	99		32(32)	75	NR	NR	NR
Frank, 2003[36]	Patients with chronic renal insufficiency, not yet dialysis dependent	Total		17	8 weeks	NR	NR	NR	NR	NR
		1	0.9% saline volume expansion	10		1	57.6+/-12.4	NR	NR	NR
		2	0.9% saline volume expansion + high-flux HD	7		2	66.8+/-9.2	NR	NR	NR
Fung, 2004[37]	Moderate to severe renal impairment: SrCr 1.69 -4.52mg/dl (149-400umol/L)	Total		91	NR		NR	NR	NR	NR
		1	IV hydration+ No drug	45		15(33)	68.0	NR	NR	NR
		2	IV hydration +NAC	46		12(26)	68.2	NR	NR	NR
Goldenberg, 2004[38]	Chronic renal insufficiency (mean [±SD] serum creatinine concentration 2.0±0.39 mg/dl)	Total		80	7 Days	NR	NR	NR	NR	NR
		1	Placebo plus IV saline 0.45%	39		8	69	NR	NR	NR
		2	Acetylcysteine plus IV saline 0.45%	41		6	71	NR	NR	NR
Gomes, 2005[39]	At risk for developing CIN: serum creatinine > 106.08 mmol/l, creatinine clearance (CrCl) , 50 ml/min, or drug treated diabetes mellitus	Total		156	48 Hours	NR	NR	NR	NR	NR
		1	Placebo	79		(43)	66.5	NR	NR	NR
		2	N-Acetylcysteine	77		(39)	63.8	NR	NR	NR
Gomes, 2012[40]	SrCr, >1.2mg/dl, GFR, <50ml/min	Total		301	48 hrs	NR	NR	NR	NR	NR
		1	Saline solution	151		(25.2)	64.5	Black: (16)	NR	NR
		2	NaHCO3	150		(30.7)	64.1	Black: (14.9)	NR	NR
Gulel, 2005[41]	Cr>1.3	Total		50	48 hrs	NR	NR	NR	NR	NR
		1	Control	25		(28)	61.5+/-11.6	NR	NR	Current: (42)
		2	NAC	25		(20)	61.4+/-12.3	NR	NR	Current: (38)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Gunebakmaz, 2012[42]	General	Total		120	5 Days	NR	NR	NR	NR	NR
		1	Saline	40		15	66.4 +/- 10.7	NR	NR	NR
		2	Saline + Nebivolol	40		11	64.1+/- 9	NR	NR	NR
		3	Saline + NAC	40		11	64.7 +/- 11.9	NR	NR	NR
Han, 2013[43]	Coronary heart disease	Total		220	48 hours	90 (41)	NR	NR	NR	NR
		1	Low-dose Oral Atorvastatin + Oral Probucol	54		25 (46)	NR	NR	NR	NR
		2	High-dose Oral Atorvastatin + Oral Probucol	73		32 (44)	NR	NR	NR	NR
		3	High-dose Oral Atorvastatin	93		33 (36)	NR	NR	NR	NR
Han, 2014[44]	Diabetes mellitus and CKD	Total		2998	72 hours	1044 (34.8)	NR	NR	NR	NR
		1	IV Normal Saline	1500		509 (43.9)	61.44	NR	NR	Current: 491 (32.7)
		2	Oral Rosuvastatin + IV Normal Saline	1498		535 (65.7)	61.45	NR	NR	Current: 463 (30.9)
Heguilen, 2013[45]	General	Total		0	3 Days	NR	NR	NR	NR	NR
		2	IV NaHCO3 in 5% dextrose in water	47		15	67.7	NR	NR	NR
		3	NAC + IV NaHCO3 in 5% dextrose in water	44		11	64.8	NR	NR	NR
		4	NAC + IV normal saline in 5% dextrose in water	42		8	69.3	NR	NR	NR
Holscher, 2008[46]	General	Total		412	30 Days	NR	NR	NR	NR	NR
		1	hydration only	139		68(16.5)	67.1	NR	NR	NR
		2	hydration plus dialysis	134		58(15.5)	66.8	NR	NR	NR
		3	hydration plus NAC	139		10(26.3)	70.5	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Hsu, 2007[47]	SrCr >=1.6mg/dl or eGFR< 40ml/mi, Diabetic patients	Total		20	5 Days	NR	NR	NR	NR	NR
		1	IV Hydration + Placebo	9		6(66.6)	48-78	NR	NR	NR
		2	IV hydration + N-acetylcysteine	11		4(36.4)	44-84	NR	NR	NR
Hsu, 2012[48]	General	Total		240	NR	NR	NR	NR	NR	NR
		1	control	103		25(24.3)	79.7	NR	NR	NR
		2	NAC	106		28(26.4)	79.7	NR		NR
Izani Wan Mohamed, 2008[49]	Renal impairment-mean SrCr 124.1+/-19.68umol/l	Total		100	48 hrs	NR	NR	NR	NR	NR
		1	IV hydration	51		9(17.6)	56.4	NR	NR	NR
		2	IV hydration + oral NAC	49		7(14.3)	57.64	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Jaffery, 2012[50]	Myocardial infarction (MI):(1) typical rise and fall of biochemical markers of myocardial necrosis (troponin-I >0.026 IU or CK-MB 4% of total CPK) with at least one of the following: (a) symptoms of coronary ischemia; (b) development of pathologic Q-waves on the electrocardiogram; or (c) electrocardiographic changes indicative of myocardial ischemia (ST segment elevation or depression), Unstable angina (UA)	Total		398	NR	146(36.7)	65.4	White: 269(67.6) Black: 108(27.1) Other: 17(4.3)	NR	Current: 84(21.1)
		1	Hydration	192		78(40.6)	65.6	White: 129(68.6) Black: 52(27.7) Other: 7(3.7)	NR	Current: 44(22.9)
		2	NAC	206		68(33)	65.6	White: 140(68) Black: 56(27.2) Other: 10(4.9)	NR	Current: 40(19.4)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Jo, 2008[51]	High risk population of patients with creatinine clearance < 60ml/min	Total		247	6 Months	NR	NR	NR	NR	NR
		1	Placebo	123		NR	66.1	NR	NR	NR
		2	Simvastatin	124		NR	65.0	NR	NR	NR
Jo, 2009[52]	CrCl ≤60 ml/min or SrCr ≥1.1 mg/dl	Total		212	6 months	47 (22)	NR	NR	NR	Current: 101 (47.6)
		2	Oral NAC + IV 0.45% Saline	106		19 (18)	64.3	NR	NR	Current: 48 (45.7)
		3	Oral Ascorbic acid + IV 0.45% Saline	106		28 (26)	65.6	NR	NR	Current: 53 (50)
Jo, 2014[53]	STEMI	Total		218	6 months	33 (15.1)	NR	NR	NR	NR
		2	Regular Atorvastatin dose	108		18 (16.7)	61	NR	NR	52 (48.1)
		3	High Atorvastatin dose	110		15 (13.6)	58	NR	NR	67 (60.9)
Kama, 2014[54]	High risk of CIN, using Mehran score (>5 points)	Total		107	1 month	48 (44.9)	71	NR	NR	NR
		1	IV Normal Saline	35		16 (32.7)	67	NR	NR	NR
		2	IV NAC in Normal Saline	36		15 (30.6)	69	NR	NR	NR
		3	IV NaHCO3 in Normal Saline	36		17 (34.7)	76	NR	NR	NR
Katoh, 2014[55]	eGFR <45 ml/min/1.73m^2	Total		66	1 month	10 (15.15)	NR	NR	NR	NR
		1	No Right Atrium Hemodiafiltration	41		8 (19.51)	75	NR	NR	NR
		2	Right Atrium Hemodiafiltration	25		2 (8.0)	80	NR	NR	NR
Kaya, 2013[56]	STEMI and creatinine clearance >60ml//min	Total		192	48 hours	49 (25.5)	NR	NR	NR	NR
		2	Oral Atorvastatin + IV Normal Saline	98		26 (26.5)	62	NR	NR	Current: 27 (27.6)
		3	Oral Rosuvastatin + IV Normal Saline	94		23 (24.5)	64	NR	NR	Current: 19 (20.2)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Kay, 2003[57]	Cr >1.2mg/dl- CrCl<60ml/min	Total		200	7 Days	NR	NR	NR	NR	NR
		1	Placebo	98		36(37)	Median: 69;Range: 48-82	NR	NR	NR
		2	NAC	102		41(40)	Median: 69;Range: 50-81	NR	NR	NR
Kefer, 2003[58]	General	Total		104	24 hrs	NR	NR	NR	NR	NR
		1	Placebo	51		12	61	NR	NR	NR
		2	NAC	53		12	61	NR	NR	NR
Khalili, 2006[59]	SrCr concentration above 1.2mg/dl or creatinine clearance of less than 60 ml/min	Total		70	72 hrs	NR	NR	NR	NR	NR
		1	Saline	35		13	74	NR	NR	NR
		2	NAC + saline	35		15	74	NR	NR	NR
		3	0	0		NR	NR	NR	NR	NR
		4	0	0		NR	NR	NR	NR	NR
Kim, 2010[60]	General	Total		166	48 hrs	NR	NR	NR	NR	All: (37)
		1	Control	86		(42)	62	NR	NR	NR
		2	NAC	80		(37)	62	NR	NR	NR
Kimmel, 2008[61]	Mild to moderately impaired kidney function: SrCr ≥ 1.2 mg/dl or a creatinine clearance < 50 ml/min	Total		54	2 Days	NR	NR	NR	NR	NR
		1	Placebo	17		(30)	66.8	NR	NR	NR
		2	NAC	19		(21)	71.5	NR	NR	NR
		3	Zinc	18		(28)	67.2	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Kinbara, 2010[62]	Stable coronary artery disease	Total		45	48 hrs	NR	NR	NR	NR	NR
		1	Hydration	15		6 (40)	70	NR	NR	NR
		2	Hydration and aminophylline	15		5 (33)	71	NR	NR	NR
		3	Hydration and N-acetylcysteine	15		6 (40)	70	NR	NR	NR
Koc, 2012[63]	CrCL≤60 ml/min or SrCr ≥1.1 mg/dl	Total		220	48 hrs	50 (23)	NR	NR	NR	NR
		1	Standard NS	60		41 (23)	64	NR	NR	NR
		2	IV NAC + High dose NS	80		19 (24)	62	NR	NR	NR
		3	High dose NS	80		17 (21)	65	NR	NR	NR
Koc, 2013[64]	Use of oral hypoglycemic agents or insulin, fasting plasma glucose levels greater than 126 mg/dL, or a random plasma glucose level of 200 mg/dL or greater.	Total		195	48 hrs	NR	NR	NR	NR	NR
		1	Normal saline	101		53(52)	62	NR	NR	Current: 26(26)
		2	NaHCO3	94		40(42)	62	NR	NR	Current: 31(33)
Kooiman, 2014[65]	CKD (eGFR <60ml/min/1.73m^2)	Total		548	2 months	227(41.4)		NR	NR	NR
		1	IV Normal saline	281		110(39.1)	72.5	NR	NR	NR
		2	IV Sodium Bicarbonate + normal saline	267		107(40.1)	71.6	NR	NR	NR
Kotlyar, 2005[66]	SrCr concentrations ≥0.13 mmol/l	Total		60	30 Days	NR	NR	NR	NR	NR
		1	IV hydration	19		2(10)	69	NR	NR	NR
		2	NAC 300mg	20		5(25)	66	NR	NR	NR
		3	NAC 600mg	21		3(14)	67	NR	NR	NR
Kumar, 2014[67]	Coronary block	Total		275	5 days	110 (22)	65	NR	NR	NR
		1	IV NS	90	NR	NR	NR	NR	NR	NR
		2	Oral NAC + IV NS	90	NR	NR	NR	NR	NR	NR
		3	Allpurinol + IV NS	95	NR	NR	NR	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Lawlor, 2007[68]	SrCr < 140 umol/l or CrCl <50 ml/min	Total		78	48 hrs	NR	NR	NR	NR	NR
		1	Placebo + IV NS	42		NR	NR	NR	NR	NR
		2	IV hydration + oral NAC	44		NR	NR	NR	NR	NR
		3	Oral hydration + oral NAC	46		NR	NR	NR	NR	NR
Lee, 2011[69]	General	Total		382	6 Months	NR	NR	NR	NR	NR
		1	Saline	189		54(28.6)	Median: 68.5;Range : 62-72	NR	NR	NR
		2	NaHCO3	193		57(29.5)	Median: 68.5; Range: 63-73	NR	NR	NR
Lehnert, 1998[70]	Stable SrCr of at least 1.4 mg/dl	Total		30	14 days	NR	NR	NR	NR	NR
		1	Saline	15		2	63.3	NR	NR	NR
		2	Hemodialysis	15		3	60.1	NR	NR	NR
Leoncini, 2014[71]	ACS	Total		504	6 months	NR	NR	NR	NR	NR
		1	No Rosuvastatin	252		87 (34.5)	66.1	NR	NR	Current: 81 (32.1)
		2	Rosuvastatin	252		86 (34.1)	66.2	NR	NR	Current: 89 (35.3)
Li, 2012[72]	Acute STEMI	Total		161	72 hrs	NR	NR	NR	NR	NR
		1	control	83		19(32.9)	66.3	NR	NR	Current: 50(60.2)
		2	atorvastatin	78		20(75.6)	66.3	NR	NR	Current: 47(60.3)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Li, 2014[73]	Coronary heart disease	Total		208	24 hours	NR	NR	NR	NR	NR
		1	Standard atorvastatin + probucol dose	55		25 (45.5)	62.3	NR	NR	Current: 19 (34.6)
		2	Large atorvastatin + probucol dose	79		33 (41.7)	60.6	NR	NR	Current: 33 (41.8)
		3	Large atorvastatin dose	74		27 (36.5)	61.0	NR	NR	Current: 36 (48.7)
Liu, 2014[74]	CKD	Total		1078	48-72 hours					
		2	Rosuvastatin + IV saline	273		57 (20.9)	65.3 (9.8)	NR	NR	NR
		3	Atorvastatin + IV saline	805		187 (23.2)	65.8 (10.3)	NR	NR	NR
MacNeill, 2003[75]	SrCr greater than or equal to 1.5 mg/dl at morning of procedure	Total		43	NR	6	72.5 +/- 9.5	NR	NR	NR
		1	Placebo	22		1	72.9 +/- 10.3	NR	NR	NR
		2	NAC	21		5	72.1 +/- 8.8	NR	NR	NR
Manari, 2014[76]	Cardiovascular: STEMI meeting inclusion criteria	Total		592	72 hours CIN; 1 year for death outcomes	149 (25.2)	NR	NR	NR	NR
		1	IV normal saline	151		38(25.1)	65	NR	NR	Current: 47(37)
		2	High-dose infusion of IV normal saline	142		32 (22.5)	65.2	NR	NR	Current: 44(31)
		3	IV standard bicarbonate	145		41 (28.5)	63.9	NR	NR	Current: 49(34)
		4	High-dose IV bicarbonate	154		38 (24.7)	65.2	NR	NR	Current: 44 (29)
Marenzi, 2003[77]	Chronic renal failure, SrCr>2.0 mg/dl	Total		114	12 Months	NR	NR	NR	NR	NR
		1	Isotonic saline	56		13 (23)	69+/-11	NR	NR	NR
		2	Hemofiltration therapy	58		12 (21)	69+/-10	NR	NR	NR
Marenzi, 2006[78]	Acute MI, ST segment elevation acute MI	Total		354	NR	NR	NR	NR	NR	NR
		1	placebo	119		22(18)	62.5	NR	NR	Current: 60(50)
		2	Standard dose NAC	115		28(24)	62.5	NR	NR	Current: 57(50)
		3	High dose NAC	118		18(15)	62.2	NR	NR	Current: 77(65)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Marenzi, 2006[79]	Chronic kidney disease (creatinine clearance ≤30 mL/min)	Total		92	NR	NR	NR	NR	NR	NR
		1	isotonic saline	30		8 (27)	71	NR	NR	NR
		2	isotonic saline plus hemofiltration after contrast exposure	31		8 (26)	72	NR	NR	NR
		3	isotonic saline plus hemofiltration before and after contrast exposure	31		11 (35)	72	NR	NR	NR
Masuda, 2007[80]	SrCr concentration greater than 1.1mg/dl or estimated gfr less than 60ml/min	Total		59	2 Days	NR	NR	NR	NR	NR
		1	NaCl (control)	29		12 (41)	76	NR	NR	NR
		2	NaHCO3	30		11 (37)	75	NR	NR	NR
Matejka, 2010[81]	SrCr > 1.47mg/dL	Total		58	4 Days	NR	NR	NR	NR	NR
		1	Control	31		9(36)	Median: 75; Range: 71-77	NR	NR	NR
		2	Theophylline	27		13(42)	Median: 75;Range: 69-80	NR	NR	NR
Merten, 2004[82]	Stable renal insufficiency undergoing diagnostic or interventional procedures requiring radiographic contrast.	Total		119	2 Days	NR	NR	NR	NR	NR
		2	NaCl	60		16 (27)	66.7	NR	NR	NR
		3	NaHCO3	0		NR	NR	NR	NR	NR
Miner, 2004[83]	Moderate renal impairment	Total		180	at least 6 months post-procedure.	NR	NR	NR	NR	NR
		1	Placebo	85		(34)	69	NR	NR	Current: (10)
		2	NAC	95		(32)	71	NR	NR	Current: (7)
Motohiro, 2011[84]	GFR <60	Total		155	1 Months	NR	NR	NR	NR	NR
		1	Cl	77		28 (36)	74 +/- 7	NR	NR	Current: 37 (48)
		2	Bicarbonate	78		19 (24)	71 +/- 9	NR	NR	Current: 48 (61)
Ochoa, 2004[85]	Documented chronic renal insufficiency (SrCr >1.8 mg/dL (males), >1.6 mg/dL (females), or a calculated creatinine clearance <50 mL/min (Cockcroft-Gault formula)	Total		80	30 Days	NR	NR	NR	NR	NR
		1	Placebo	44		26(59)	70	NR	NR	NR
		2	NAC	36		20(56)	73	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Oldemeyer, 2003[86]	Creatinine clearance <50ml/min, or SrCr >1.2 mg/dl	Total		96	48 hrs	NR	NR	Reported	NR	NR
		1	Placebo	47		21	75+/-8	White: 45(96) Black: 2(4)	NR	NR
		2	NAC	49		22	77+/-9	White: 48(98) Black: 1(2)	NR	NR
Ozcan, 2007[87]	General	Total		264	2 Days	(25.4)	69;Range: 40-87	NR	NR	NR
		1	IV normal saline	88		(25)	70;Range: 40-84	NR	NR	NR
		2	Oral NAC + IV normal saline	88		(23.9)	67;Range: 48-87	NR	NR	NR
		3	IV NaHCO3 in 5% dextrose in water	88		(27.3)	68;Range: 43-86	NR	NR	NR
Ozhan, 2010[88]	General	Total		130	48 hrs	53	54 +/-10	NR	NR	NR
		2	NAC	70		30	55+/-8	NR	NR	NR
		3	NAC + Atorvastatin	60		23	54+/-10	NR	NR	NR
Patti, 2011[89]	Acute coronary syndromes, unstable angina or non-ST-segment elevation myocardial infarction	Total		241	48 hrs	NR	NR	NR	NR	NR
		1	Placebo	121		25(21)	65 +/- 10	NR	NR	Current: 29(24)
		2	Atorvastatin	120		29(24)	65 +/- 10	NR	NR	Current: 39(32)
Poletti, 2007[90]	SrCr concentration > 106 µmol/L (1.2 mg/dL)	Total		100	4 Days	NR	NR	NR	NR	NR
		1	Hydration plus placebo	50		14(33)	72.7	NR	NR	NR
		2	Hydration plus N-acetylcysteine	50		18(41)	69.5	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Qiao, 2015[91]*	T2DM, mild to moderate CKD	Total		120	72 hours					
		1	IV saline	60		NR	NR	NR	NR	NR
		2	IV slaine + rsuvastatin	60		NR	NR	NR	NR	NR
Quintavalle, 2012[92]	General	Total		410	7 Days	NR	NR	NR	NR	NR
		1	Control	208		88(42)	70; Range: 8	NR	NR	NR
		2	Atorvastatin	202		99(49)	70; Range: 6	NR	NR	NR
Ratcliffe, 2009[93]	General	Total		78	7 Days	NR	NR	NR	NR	NR
		1	IV normal saline in 5%dextrose in water	15		6(40)	64	White: (20) Black: (27) Latino: (33) Asian/Pac: (20)	NR	NR
		2	IV and oral NAC + IV normal saline in 5% dextrose in water	21		10(48)	65	White: (10) Black: (33) Latino: (33) Asian/Pac: (20)	NR	NR
		3	IV NaHCO3 in 5% dextrose in water	19		8(42)	67	White: (6) Black: (44) Latino: (33) Asian/Pac: (24)	NR	NR
		4	IV and oral NAC + IV NaHCO3 in 5% dextrose in water	23		7(30)	65	White: (14) Black: (29) Latino: (43) Asian/Pac: (17)	NR	NR
Rashid, 2004[94]	Peripheral vascular disease	Total		94	7 days	34 (36.2)	NR	NR	NR	NR
		1	IV Normal Saline	48		15 (31.3)	68.8	NR	NR	NR
		2	IV Normal Saline + Oral NAC	46		19 (41.3)	72.1	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Reinecke, 2007[95]	General	Total		424	Median 553 Days Range 63-1316 days	NR	NR	NR	NR	NR
		1	Hydration only	140		24(17.1)	67.9	NR	NR	Ever: 80(57.1)
		2	Hydration + Dialysis	138		24(17.4)	67.9	NR	NR	Ever: 74(53.6)
		3	Hydration + NAC	146		25(17.1)	66.7	NR	NR	Ever: 75(51.4)
Sadat, 2011[96]	General	Total		40	7 Days	NR	75	NR	NR	NR
		1	IV Hydration only	19		NR	NR	NR	NR	NR
		2	Hydration+NAC	21		NR	NR	NR	NR	NR
Sandhu, 2006[97]	General	Total		106	48 hrs		NR	NR	NR	NR
		1	Control	53		22	66+/-13.9	NR	NR	NR
		2	NAC	53		18	69.3+/-14.2	NR	NR	NR
Sanei, 2014[98]	General	Total		236						
		1	Placebo	121		36 (29.8)	58.7 (9.3)	NR	NR	NR
		2	High dose atorvastatin	115		38 (33)	58.1 (10.4)	NR	NR	NR
Sar, 2010[99]	Diabetic	Total		45	72 hrs	21 (47)	NR	NR	NR	NR
		1	IV Normal Saline	20		9 (45)	53.5	NR	NR	NR
		2	Oral NAC + IV Normal Saline	25		12 (48)	60.0	NR	NR	NR
Seyon, 2007[100]	Renal dysfunction with baseline creatinine equal to or greater than 125 mol/L (1.4 mg/dL) for males or equal to or greater than 115 mol/L (1.3 mg/dL) for females	Total		40	NR	NR	NR	NR	NR	NR
		1	Placebo+hydration	20		6 (30)	74.7+/-9.7	NR	NR	NR
		2	N-Acetylcysteine + hydration	20		8 (40)	76.4+/-5.9	NR	NR	NR
Shavit, 2009[101]	Patients with CKD stage III–IV (eGFR 15–60mL/min	Total		93	48 hrs	NR	NR	NR	NR	NR
		1	IV NaHCO3 in 5% dextrose in water	51		8(16)	71	NR	NR	Current: 11(22)
		2	Oral NAC + intravenous normal saline	42		11(30)	71	NR	NR	Current: 9(25)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Shehata, 2015[102]	chronic stable angina; mild or moderate CKD	Total		130	72 hours					
		1	Placebo (NAC)	65		33 (44)	57 (5)	NR	NR	NR
		2	Atorvastatin	65		30 (47)	55 (6)	NR	NR	NR
Spargias, 2004[103]	SrCr ≥1.2 mg/dl	Total		231	5 days	18 (8)	NR	NR	NR	Current: 47 (20)
		1	Placebo + IV Normal Saline	113		7 (6)	64	NR	NR	Current: 23 (21)
		2	Oral Ascorbic Acid + IV Normal Saline	118		11 (9)	67	NR	NR	Current: 24 (21)
Shyu, 2002[104]	SrCr concentrations 2.0 mg/dl and 6.0 mg/dl or rates of creatinine clearance (CrCl) 40 ml/min and 8 ml/min	Total		120	7 Days	NR	NR	NR	NR	NR
		1	Placebo + 0.45% saline	60		21(52.5)	70; Range: 63-77	NR	NR	NR
		2	NAC + 0.45% saline	60		18(42.8)	70; Range: 63-77	NR	NR	NR
Tanaka, 2011[105]	STEMI with PCI	Total		82	72 hrs	NR	NR	NR	NR	NR
		1	Placebo	38		7 (18)	60.5 +/- 14	NR	NR	Current: 9 (24)
		2	NAC	38		7 (18)	62.8 +/- 13	NR	NR	Current: 14 (42)
Tepel, 2000[106]	Known h/o CKD with stable creatinine defined as, SrCr concentration above 1.2 mg per deciliter (106 µmol per liter) or creatinine clearance of less than 50 ml per minute (0.8 ml per second)	Total	NR	83	6 days	36 (43)	NR	NR	NR	NR
		1	placebo and saline	42		19 (45)	65	NR	NR	NR
		2	Acetylcysteine (600 mg orally twice daily) and 0.45 percent saline intravenously	41		17 (41)	66	NR	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Thayssen, 2014[107]	STEMI	Total		715	30 Days	165(23.1)	NR	NR	NR	NR
		1	IV Normal Saline	181		36(19.9)	63	NR	NR	Current: 89(51.1)
		2	IV Normal Saline + oral NAC	176		49(17.8)	63	NR	NR	Current: 82 (48.8)
		3	IV Normal Saline + IV NaHCO3	181		42(23.2)	62	NR	NR	Current: 88(51.2)
		4	IV Normal Saline + oral NAC + IV NaHCO3	177		38(21.5)	63	NR	NR	Current: 79(46.5)
Thiele, 2010[108]	Acute Myocardial Infarction, ST-segment elevation myocardial infarction patients	Total		251	one 6 months outpatient visit for all patients.	80(32)	NR	NR	NR	NR
		1	Placebo	125		43(34)	Median: 68;Range: 56-76	NR	NR	Current: 54(43)
		2	NAC	126		37(29)	Median: 68;Range: 57-75	NR	NR	Current: 40(32)
Toso, 2010[109]	General	Total		304	1 Month	NR	Median: 75	NR	NR	NR
		1	Placebo	152		60(40)	76 +/-7	NR	NR	NR
		2	Atorvastatin	152		48(32)	75+/-8	NR	NR	NR
Traub, 2013[110]	General	Total		399	72 hours	237 (59.4)	NR	NR	NR	NR
		1	IV Normal Saline	199		113 (57)	59.7	White: 142 (71) Black: 47 (24) Latino: 0 (0) Asian: 2 (1) Other: 8 (4)	NR	NR
		2	IV NAC + IV Normal Saline	200		124 (62)	61.5	White: 137 (69) Black: 50 (25) Latino: 1 (1) Asian: 1 (1) Other: 11 (6)	NR	NR

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Ueda, 2011[111]	Cr > 1.1 mg/dl - eGFR <60ml/min	Total		60	2 Days		75+/- 10	NR	NR	NR
		1	NaCl	30		7 (23)	77+/- 9	NR	NR	NR
		2	NaHCO3	30		NR	NR	NR	NR	NR
Vasheghani-Farahani, 2010[112]	CHF	Total		72	2 Days	NR	NR	NR	NR	NR
		1	Saline	36		7(19.4)	61.4	NR	NR	NR
		2	Bicarbonate	36		8(22.2)	61.4	NR	NR	NR
Vogt, 2001[113]	Chronic stable renal failure: >2.3 mg/dl SrCr	Total		113	NR	NR	NR	NR	NR	NR
		1	IV saline	58		23 (40)	69+/-10	NR	NR	NR
		2	IV saline/Hemodialysis	55		22 (40)	70+/-10	NR	NR	NR
Wang, 2008[114]	General	Total		46	24 hours	19 (41.3)	NR	NR	NR	NR
		1	IV Normal Saline	23		9 (39.1)	69	NR	NR	Current: 1 (4.3)
		2	IV NAC + IV Normal Saline	23		10 (43.5)	66	NR	NR	Current: 3 (13.0)
Webb, 2004[115]	GFR < 50 ml/min	Total		487	Median: 3 Days	NR	NR	NR	NR	NR
		1	Placebo	245		(38.0)	70.0	NR	NR	Current: (9.4)
		2	NAC	242		(40.5)	70.8	NR	NR	Current: (11.3)
Xinwei, 2009[116]	Acute Coronary syndrome	Total		228	48 hours	NR	NR	NR	NR	NR
		2	Simvastatin 20	115		67 (58)	NR	NR	NR	NR
		3	Simvastatin 80	113		79 (70)	NR	NR	NR	NR
Yeganehkhah, 2014[117]	High Risk CIN	Total		150	48hrs	78 (52)	59.2	NR	NR	NR
		1	IV NS	50		28 (56)	58.5	NR	NR	NR
		2	NaHCO3 + IV NS	50		25 (50)	58.1	NR	NR	NR
		3	Oral NAC + IV NS	50		19 (38)	60.9	NR	NR	NR
Yun, 2014[118]	General populations receiving PCI	Total		824	72 hours					
		1	IV normal saline	416		130 (31)	63.6 (12.5)	NR	NR	NR
		2	IV normal saline + Risovustatin	408		154 (37.8)	64.3 (11.7)	NR	NR	NR
Zhang, 2015[119]	T2DM, CKD stage 2 or 3 (moderate contrast volume)			712						
		1	Placebo	355		92 (25.9)	61.4 (8.7)	NR	NR	122 (34.4)
		2	Rosuvastatin	357		113 (31.6)	61.8 (8.5)	NR	NR	114 (31.9)

Evidence Table E-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status
Zhang, 2015[119]	T2DM, CKD stage 2 or 3 (high contrast volume)			220						
		1	Placebo	102		26 (25.4)	61.5 (8.1)	NR	NR	43 (42.2)
		2	Rosuvastatin	118		31(26.3)	61 (9.2)	NR	NR	41 (34.7)
Zhou, 2012[120]	eGFR <60 ml/min/1.73 m^2 or SrCr ≥1.1 mg/dl	Total		156	2 days	58 (37)	NR	NR	NR	Current: 80 (51)
		1	IV Normal Saline	82		35 (43)	71.4	NR	NR	Current: 39 (47.6)
		2	IV and Oral Ascorbic Acid + IV Normal Saline	74		23 (31)	71.8	NR	NR	Current: 41 (55.4)

ACS=Acute Coronary Syndrome, AVH= amlodipine valsartan hydration group, CCS=Canadian Cardiovascular Society, CHF=Chronic Heart Failure, CIN=Contrast Induced Nephropathy, CKD=Chronic Kidney Disease, CK-MB=Creatine Kinase MB, CPK=Creatine Phosphokinase, Cr=Creatinine, CrCl=Creatinine Clearance, CRF=Chronic Renal Failure, eGFR=Estimated Glomerular Filtration Rate, GFR=Glomerular Filtration Rate, H=hydration group, HD=Hemodialysis, h/o=history of; hrs=hours; ICU=Intensive Care Unit, IU=International Units, IV=Intravenous, IVF=Intravenous Fluid, Mg/dl=milligram per deciliter, Mg/kg/hour=Milligram per kilogram per hour, Mg/kg=milligram per kilogram, MI=Myocardial Infarction, ml/min/1.73m^2=milliliter per minute per 1.73 meter squared, Ml/min=milliliter per minute, Mmol/l=millimole per liter, N=Sample Size, NAC=N-acetylcysteine, NR=Not Reported, NSTEMI=non-ST-segment elevation-mycordial infarction, OHT=Orthotopic Heart Transplantation, PCI=Percutaneous Coronary Intervention, SCr=SrCr, SD=Standard Deviation, SrCr=SrCr, STEMI= ST-segment elevation-mycordial infarction, UA=Unstalbe Angina, Ug/kg/min=microgram per kilogram per minute, Umol/l=micromole per liter
* if there is no “Arm 1” there is no control group.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Abaci, 2015[1]	2	RCT/ controlled	No	2012-2013	Inpatient	NR	No acute or end-stage renal failure. No history of coronary artery disease, congestive heart failure, coronary occlusion, allergy to contrast media, contrast within 14 days of procedure. No current statin treatment, or contraindications to statin treatment. No sever comorbidities, or pregnancy.
Acikel, 2010[2]	2	RCT/ Controlled	Yes	NR	Inpatient (including ICU)	Single-center	Undergoing Coronary Angiography; a low-density lipoprotein (LDL) level of more than 70 mg/dl and receiving no cholesterol-lowering medication; No chronic renal failure requiring dialysis and/or moderate-to-severe decrease in glomerular filtration rate (GFR) defined as less than60 ml/min per 1.73 m2; No chronic liver disease or failure; No stage III–IV heart failure; acute coronary syndromes; No contrast exposure history in 3 months preceding the procedure; No active infections; No systemic inflammatory diseases; No malignancies; No hypothyroidism or hyperthyroidism; No use of other antilipidemic therapies (except statins), Nacetylcysteine, theophylline, aminophylline, nonsteroidal anti-inflammatory drugs, vitamin supplements, antibiotics, or steroids.
ACT, 2011[3]	2	RCT/ Controlled	Yes	2008 to 2010	NR	Multi-center	PCI, mild-mod- Cr < 176 umol/L, Other Risk factors, GFR ≥60 to ≤89 and ≥30 to ≤59 No diagnostic coronary angiography due to either insignificant coronary lesions or bypass surgery. SrCr <176 μmol/L. No congestive heart failure (NYHA stage IV), or renal artery stenosis diagnosed with renal angiography incidentally during coronary angiography. No allergies to contrast agent or ACEI intolerance. No autoimmune disease, end-stage renal failure requiring dialysis, administration of contrast medium (CM) within the previous 6 days and within the following 2 days, or pregnancy.
Albabtain, 2013[4]	2	RCT/Controlle d	Yes	NR	NR	Single-center	Undergoing coronary angiography or PCI; >18 years of age; Serum creatinine ≥1.3 mg/dl or on diabetes mellitus medication; No known acute renal failure; No end-stage renal disease requiring dialysis; No intravascular administration of contrast medium within the previous 6 days; No anticipated re-administration of contrast medium within the following 6 days; No use of vitamin C supplements on a daily basis during the week before the procedure; No inability to administer the study medication at least 2 hours before the procedure.
Alexopoulos, 2010[5]	2	RCT/ Controlled	Yes	NR	NR	NR	Undergoing nonemergent coronary angiography; SrCr ≥1.2 mg/dL (106umol/L); No known acute renal failure or end-stage renal disease requiring dialysis; had not received an intravascular administration of contrast medium within the previous 6 days or for whom readministration of contrast medium within the following 6 days was anticipated; had not ingested vitamin C supplements on a daily basis during the week before the procedure.
Alioglu, 2013[6]	2	RCT/ Controlled	No	NR	NR	NR	>18 years, elective cardiovascular procedures; not on dialysis; NO patients with uncontrolled hypertension, SrCr levels of more than 7 mg/dL, severe valvular heart disease, autoimmune disease, chronic or acute infectious disease, emergency catheterization, recent exposure to radiographic contrast within 10 days, medication with NSAID or metformin up to 3 days before entering study, allergy to radiographic contrast or NAC
Allaqaband, 2002[7]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	NR	Scheduled to undergo cardiovascular intervention with radio contrast agent; baseline creatinine > 1.6 mg/dl or estimated CrCl 60 ml/min

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Amini, 2009[8]	2	RCT/ Controlled trial	No	2006	Inpatient (including ICU)	Single-center	>18yrs; elective diagnostic coronary angiography; disease, defined as SrCr concentration ≥ 1.5 mg/dL for men and ≥ 1.4 mg/dL for women; Other Risk factors, history of diabetes mellitus for at least one year; no patients with acute coronary syndrome requiring primary or rescue coronary intervention within less than 12 h, no patients with cardiogenic shock, current peritoneal or hemodialysis, or a known allergy to NAC
Aslanger, 2012[9]	2	RCT/ Controlled	No	2007 to 2009	NR	Single-center	>30years, Primary angioplasty,; Other Risk factors, ST-segment elevation myocardial infarction, angioplasty within 12 hrs of symptoms No allergies to NACNot on dialysis
Awal, 2011[10]	2	Non-RCT	No	2009 to 2010	Outpatient	Single-center	> 20 years Coronary angiography and intervention; SrCr <2 mg/dl. No acute myocardial infarction, unstable coronary syndrome, cardiogenic shock, history of end-stage renal failure or being on dialysis. No N-acetyl cysteine use and history of intravenous contrast media administration within the previous 10 days.
Azmus, 2005[11]	1,2	RCT/ Controlled	No	2001 to 2002	NR	NR	>70 years; Other Risk factors, Diabetic, SrCr levels >1.3 mg/dl. No dialyzed patients, no patients with acute renal failure
Baker, 2003[12]	2	RCT/ Controlled	Yes	NR	NR	Multi-center	Scheduled for coronary angiography; SrCr concentration >1.36 mg/dl or creatinine clearance <50 ml/min. No acute renal failure or end-stage renal failure on dialysis. Have not received a non-steroidal anti-inflammatory agent within 24 hrs of study. Those with blood pressure >90mm HG. No hemodynamically significant valvular heart disease. No signs of cardiac failure.
Baranska-Kosakowska, 2007[14]	2	RCT/ Controlled	Yes	2005 to 2006	NR	Single-center	Undergoing coronary angiography; post orthotopic heart transplant patient
Baskurt, 2009[13]	2	RCT/ Controlled	No	2008 to 2010	NR	Multi-center	>70year, coronary or peripheral arterial diagnostic intra- vascular angiography or percutaneous intervention chronic renal failure (stable SrCr concentrations >132.6 umol/L, at least 1 risk factor for contrast-induced acute kidney injury: age > 70 years, chronic renal failure (stable SrCr concentrations > 132.6 mol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction < 0.45, or hypotension. no patient on dialysis and those with ST-segment elevation myocardial infarction undergoing primary angioplasty, no woman pregnant, breastfeeding, or aged 45years and not using contraceptive methods
Beyazal, 2014[15]	1	Non-RCT	No	NR	NR	Single-center	Undergoing PCAG, serum creatinine values between 1.1 and 3.1 mg/dL. No serum creatinine values outside the specified range,no previously diagnosed multiple myeloma,no distinctive heart failure, no uncontrolled hypertension (systolic4160 mmHg,diastolic4100 mmHg),no patients who received the contrast agent within the last 3 days, no known allergic reaction to the contrast agent, have not received N-acetyl cysteine, dopamine or mannitol during the month prior to the study and no pregnant women. No patients using b-blockers were included from the group that received diltiazem.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Bilasy, 2012[16]	2	RCT/ Controlled	No	2009 to 2010	Inpatient (including ICU)	Single-center	Elective coronary angiography (CA) and/or angioplasty; moderate risk for CIN as defined by Mehran risk score, no subjects with unstable SrCr(defined as a difference of > 0.1 mg/dL between baseline "at admission" and preprocedural levels),no patients with recent intravascular administration of CM within 1 month, shock, end-stage renal disease on hemodialysis, and known hypersensitivity to NAC or theophylline, Serious cardiac arrhythmias, seizures, and acute renal failure
Boccalandro, 2003[17]	2	RCT/ Controlled	No	2000 to 2001	Inpatient (including ICU)	Single-center	Elective cardiac catheterization, SrCr 1.2 mg/dl or a creatinine clearance 50 ml who underwent elective cardiac catheterization and received 1 cc/kg of radiographic contrast, no acute renal failure or end-stage renal disease, not receiving oral theophylline, mannitol, furosemide, or dopamine, or undergoing renal angioplasty or renal angiogram
Boscheri, 2007[18]	2	RCT/Controlle d	Yes	NR	NR	Single-center	Undergoing coronary angiography or angioplasty; known chronic renal failure; stable serum creatinine >120 umol/l or 1.4 mg/dl; No myocardial infarction in the past 3 months; NO cardiogenic shock; No use of vasopressors; Ejection fraction ≥25%; No acute renal failure; No current peritoneal dialysis or hemodialysis; Not pregnant; No exposure to contrast dye or medication with NAC up to 72 hours prior to study entry.
Boucek, 2013[19]	1,2	RCT/ Controlled	No	2008 to 2012	Inpatient (including ICU)	Single-center	Planned procedure using IV or IA contrast media; screening SrCr >100umol/L, Other Risk factors, Diabetic, Not on dialysis SrCr < 500umol/Lot an emergency procedure;no acute kidney injury (> 50 umol/l) 24 hrs pre procedure;no volume overload with left ventrictular failure;systolic blood pressure < 180 mmHg;hemodynamic stability with systolic blood pressure > or = to 90 mmHg and diastolic blood pressure > or = to 50 mmHg;no contrast within 48 hrs of procedure;not pregnant;no other preventative CIN measures
Brar, 2008[20]	2	RCT/ Controlled trial	No	2006 to 2007	Inpatient (including ICU)	Single-center	>18yrs; coronary angiography; Stable renal disease (not defined); other inclusion criteria were an estimated glomerular filtration rate (GFR) of 60 mL/min per 1.73 m 2 or less,and at least 1 of diabetes mellitus, history of congestive heart failure, hypertension (140/90 mm Hg or treatment with an antihypertensive medication), or age older than 75 years.;Exclusion criteria included inability to obtain consent, receipt of a sodium bi-carbonate infusion prior to randomiza tion, emergency cardiac catheterization, intra-aortic balloon counter- pulsation, dialysis, exposure to radiographic contrast media within the preceding 2 days, allergy to radiographic contrast media, acutely decompensated congestive heart failure, severe valvular abnormality (eg, severe aortic stenosis or mitral regurgitation), single functioning kidney, history of kidney or heart transplantation, and change in estimated GFR of 7.5% or more per day or a cumulative change of 15% or more over the prior 2 or more days Patients were further stratified according to diabetes and N-acetylcysteine use

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Briguori, 2002[21]	2	RCT/ Controlled	No	2006 to 2009	NR	Multi-center	>1<16 years,clinically indicated contrast-enhanced multi-detector computer tomography (MDCT), normal renal function (creatinine clearance >60 ml/min/1.73 m2, calculated by the Schwartz's formula),no case of pregnancy or known hypersensitivity to iodine-containing compounds, not received any iodinated contrast agent within 7 days before the administration of the investigational product, not scheduled to receive an iodinated contrast agent within 72 h after administration of the investigational product, not received any nephrotoxic medication (chemotherapeutic agents, diuretics or biguanide), no surgery planned within 72 h after the administration of the contrast agent.
Brigouri, 2007[22]	2	RCT/ Controlled	No	2005 to 2006	NR	NR	>18 years, stable serum creatinine concentration >2.0mg/dl and/or eGFR <40ml/min/1.73m^2. No serum creatinine 8mg/dl, history of dialysis, multiple myeloma, pulmonary edema, ami, recent exposure to contrast (2 days of study), pregnancy, or had administration of theophylline, dopamine, mannitol or fenoldopam.
Brueck, 2013[23]	2	RCT/ Controlled	No	2004 to 2008	Inpatient (including ICU)	Single-center	diagnostic or interventional cardiac catheterization, stable baseline SrCr concentration of ≥1.3 mg/dL, no SrCr measurements ≥0.3 mg/dL change in the 7 days prior to angiography, no exposure to contrast agents or nephrotoxic medication (ie, non-steroidal anti-inflammatory drugs, aminoglycoside, vancomycin) within the week prior to cardiac catheterization, no renal transplant recipients, plasmocytoma, oxalosis, nephrolithiasis, hyperthyroidism, unavailability of adequate time prior to angiography to perform the study procedures, no previously known insensitivity to N-acetylcysteine or ascorbic acid, no pregnant and breast feeding women, as well as those with child-bearing potential not using an approved method of contraception
Burns, 2010[24]	1	RCT/ Controlled	No	2002 to 2005	Inpatient (including ICU)	Multi-center	had a central venous access and a foley catheter, required a contrast-enhanced CT of any organ system; a SrCr of106 µmol/l and/or urea 6 mmol/l, urine output of < 0.5 cc/kg over 4 h or an increase in SrCr of 50 µmol/l in 24 h. Creatinine kinase <5000. No presence of myoglobunaria. No allergies to NAC or contrast. No serious illness with imminent threat of death. Not pregnant. No radiogenic shock. No nephritic, nephrotic or pulmonary-renal syndromes. No post-renal etiology of renal impairment. No previous renal transplant or solitary kidney. SrCr < 200 umol/l.
Buyukhatipoglu, 2010[25]	2	RCT/ Controlled	No	NR	NR	Single-center	undergoing PCI; Coronary artery disease; NO acute coronary syndrome; NO coexisting cardiac disease; no evidence of liver, kidney, or respiratory disease; no diabetes mellitus; no malignancy; no infectious, inflammatory, or infiltrative disorder; no unregulated hypertension; no reduced left ventricular ejection fraction, or any findings or history of congestive heart failure; no recent use (within 48 h) of any drug with antioxidant properties;no regular alcohol use or alcohol use within the previous 48 hournone
Carbonell, 2007[26]	2	RCT/ Controlled	No	2002 to 2005	Inpatient (including ICU)	Single-center	Cardiac catheterization; Cr<1.4, no chronic renal failure, no acute renal dysfunction, no hemodynamic instability (systolic blood pressure <90 mm Hg), no known allergy to N - acetylcysteine or to contrast agents, no untreated gastrointestinal bleeding and/or previous treatment with theophylline, mannitol or nephrotoxic antibiotic

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Carbonell, 2010[27]	2	RCT/ Controlled	No	2002 to 2006	Inpatient (including ICU)	Single-center	Coronary angiography; Cr >1.4, no hemodynamic instability (systolic blood pressure <90 mm Hg), no known NAC or contrast agent allergies, no untreated gastrointestinal bleeding, and/ or previous antibiotic treatment with theophylline, mannitol or nephrotoxic drugs
Castini, 2010[28]	2	RCT/ Controlled trial	No	NR	NR	NS	>18; cardiac aniogram; baseline creatinine level ≥1.2mg/dL; Stable SrCr: </= 4mg/dl; No history of dialysis; no multiple myeloma; no pulmonary edema; no cardiogenic shock; no acute MI; no emergency catheterization; no previous exposure to CM or NAC within 7 days; no previous enrollment in same or other protocols; not pregnant; no administration of theophylline, mannitol, dopamine, dobutamine, NSAIDS, or fenoldopam.
Chousterman, 2013[30]	1,2	Non-RCT	No	NR	Inpatient (including ICU)	Multi-center	All patients admitted into IOCU needing computed tomography or angiography; Patients free of dialysis. Available SrCr within 48 hrs before and 72 hrs after the radiological exam.
Chousterman, 2011[29]	1,2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Multi-center	>18, needing computed tomography or angiography, No previous iodinated contrast within 3 days after index procedure.For NAC group, patient must have received at least one 600mg dose before examination.
Demir, 2008[31]	1	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	CT, No diabetes, no chronic renal failure, no uncontrolled hypertension or hypotension, no pregnancy, no ESRD, no renal transplantation, no dialysis history, no sensitivity to CM, no nephrotoxic drug use (NSAIDs, aminoglycoside, etc)
Durham, 2002[32]	2	RCT/ Controlled	No	NR	NR	Multi-center	>18years, coronary angiography and/or PCI, mild to moderate renal dysfunction with SrCr ≥ 1.1 mg/dL or creatinine clearance ≤ 60 mL/min, Does not have contrast-agent hypersensitivity, pregnancy-lactation, decompensated heart failure, pulmonary edema, emergency catheterization, acute renal failure or end-stage renal failure
Erturk, 2014[34]	2	RCT/ Controlled	No	2010 to 2012	Inpatient (including ICU)	Single-center	>21 years; undergoing an intra-arterial procedure (not specified); moderate to severe renal dysfunction; eGFR < 60 ml/min/1.73m2; no dialysis; eGFR > 15 ml/min/1.73m2; SBP<160; DBP<110; no CM contrast within 7 days; no acute chronic inflammatory disease; no NSAIDS or metformin for 2 days prior to procedure; not pregnant; no known allergy to contrast agent or NAC; not taking fenoldopam, mannitol, dopamine, or theophylline.
Ferrario, 2009[35]	2	RCT/ Controlled	No	NR	NR	Single-center	>18 years, coronary or peripheral angiography/angioplasty, CVD; NYHA III-IV; creatinine clearance <55ml/min, No ongoing acute myocardial infarction or acute coronary syndrome. No need for theophylline, dopamine, fenoldopam, mannitol or nephrotoxic drugs within 1 week of procedure. No clinical signs of dehydration and systematic hypotension.
Frank, 2003[36]	2	RCT/ Controlled trial	No	2000 to 2001	Inpatient (including ICU)	Single-center	>18; coronary angiography; not requiring HD; Stable SrCr (> 3mg/dl); no allergy to contrast medium; not pregnant; no acute renal failure
Fung, 2004[37]	2	RCT/ Controlled	No	NR	NR	NR	elective coronary angiography or intervention; SrCr level of 1.69 to 4.52 mg/dL (149 to 400 umol /L), with at least 2 serum cr measurements within 1 month before coronary angiography, with fluctuation < 15% to confirm stable renal function before recruitment, No known allergy to NAC or contrast agents; Absence of cardiogenic shock, current; dialysis therapy, and concomitant use of dopamine, theophylline or mannitol.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Goldenberg, 2004[38]	2	RCT/ Controlled	No	NR	NR	NR	Angiography Cr <1.5mg/dl and eGFR >70ml/min. No allergies to contrast media No renal insufficiency
Gomes, 2005[39]	2	RCT/ Controlled	No	2001 to 2003	Inpatient (including ICU)	Multi-center	Other Risk factors SrCr > 106.08 mmol/l, CrCl , 50 ml/min, or drug treated diabetes mellitus, no use of radiographic contrast media within 21 days of randomization, no current dialysis, no hemodynamic instability before the procedure (systolic blood pressure (90 mm Hg or diastolic blood pressure (60 mm Hg), and no history of sensitivity to N-acetylcysteine
Gomes, 2012[40]	2	RCT/ Controlled	No	NR	NR	Multi-center	Other Risk factors, SrCr >1.2mg/dl, or GFR <50 ml/min, No history of dialysis, no cardiac insufficiency class iii-iv, no emergency procedures, no use of contrast < 21 days ago.
Gulel, 2005[41]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	Coronary angiography without intervention; Cr >1.3
Gunebakmaz, 2012[42]	2	RCT/ Controlled trial	No	2008 to 2009	NR	Single-center	coronary angiography or ventriculography; Baseline Creatinine > 1.2 mg/dl; Not on dialysis, no recent exposure to contrast media or nephrotoxic agents with 7 days of study; No urgent percutaneous coronary interventions; Do not require loop diuretics; No theophylline/aminophylline, dopamine or contraindications for beta blockers; hemodynamically stable
Han, 2013[43]	1,2	RCT/ Controlled trial	Yes	NR	NR	NR	Have coronary heart disease
Han, 2014[44]	2	RCT/ Controlled trial	Yes	2008 to 2011	NR	Multi-center	18-75 years of age; undergoing coronary/peripheral artierial diagnostic angiography, left ventriculography or PCI; T2DM, defined by American Diabetes Association; CKD; did not receive statin treatment for at least 14 days prior to CM administration; no CM sensitivity; no T1DM; no ketoacidosis or lactoacidosis; CKD stage 2 or 3 only; no STEMI within 4 weeks of study; No class IV NYHA classification; hemodynamically stable; no CM 2 weeks prior to randomization; LDL >/= 1.82mmol.L; no hepatic dysfunction; no thyroid insufficiency; no renal artery stenosis
Heguilen, 2013[45]	1,2	RCT/ Controlled	No	NR	other	Single-center	> 18years, scheduled for cardiac catheterization or arteriographic procedure, Stable SrCr >1.25 mg/dL or Cockcroft-Gault-estimated creatinine clearance <45 ml/min non-emergency catheterization; without pulmonary edema; no preexisting dialysis; non recent exposure to CM; no history of multiple myeloma; controlled hypertensives; without hemodynamic instability; not being treated with the following medications: dopamine, mannitol, fenoldopam, aminophylline, theophylline, ascorbic acid or NAC; Non pregnant or childbearing women; or not hypersensitive to CM or NAC. The SCr shouldn't be [4.5 mg/dl ([364.5 lmol/l) or no change in SCr of at least 0.5 mg/dl (44.2 lmol/l) within the previous week.
Holscher, 2008[46]	2	RCT/ Controlled	No	NR	NR	Single-center	>14years and <79years, coronary angio-PCA- CT scan- IV pyelography; No acute renal failure, maintenance dialysis, history of acute myocardial infarction, left ventricular ejection fraction (EF) ≤ 25%, allergy to contrast media, pregnancy, contraindications for theophylline use such as untreated high-grade arrhythmia or history of seizure, or use of acetylcysteine.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Hsu, 2007[47]	2	RCT/ Controlled	No	2003 to 2005	Outpatient	NR	Cardiac angiography; SrCr >1.6 mg/dL or eGFR <40ml/min, Other Risk factors, diabetes, left ventricular ejection fracture >40%, no acute coronary syndrome requiring immediate intervention, no end stage renal failure or unstable renal function, no shock, no unstable renal function, no active UTI, no acute renal failure or dialysis within last 30days, no heavy proteinuria (urinary protein >or = 300mg/dl) no gross hematuria, no active congestive heart failure, no exposure to contrast or other nephrotoxic agent in past 30days, no exposure to contrast media other than iohexol, no exposure to aminophylline, dopamine, or mannitol 1week before procedure, no SrCr measurement variation >15% 30days before procedure No HD and ARF
Hsu, 2012[48]	1	Non-RCT	No	2009 to 2010	Emergency department	Single-center	Abdominal or chest contrast-enhanced computed tomography, no long-term hemodialysis or peritoneal dialysis, Not received another dose of contrast medium within 72 hrs, no known allergy to N-acetyl- cysteine (NAC)
Huber, 2002[121]	1,2	RCT/ Controlled	No	NR	NR	Single-center	Stable serum cr of 1.3 mg/dL (114.3 umol /L) or higher, Non-pregnant women. No contraindication to theophylline such as untreated high-grade arrhythmia or history of seizure. Patients need to have a difference between measured baseline creatinine and creatinine obtained in the preceding 2 days of less than or equal to 0.3 mg/dl.
Izani Wan Mohamed, 2008[49]	2	RCT/ Controlled	No	2006 to 2007	Inpatient (including ICU)	Single-center	Coronary angiography; renal impairment-mean SrCr 124.1+/-19.68umol/l, calculated creatinine clearance between 40-90ml/min. No severe renal failure , No acute or reversible component of renal failure, no severe peptic ulcer disease, no history of allergy to N- acetyl cysteine No0 severe asthma, not pregnant or breast feeding.
Jaffery, 2012[50]	2	RCT/ Controlled	No	2007 to 2010	Inpatient (including ICU)	Single-center	>18 years, coronary angiography and/or percutaneous coronary intervention; NO end-stage renal disease (ESRD) requiring dialysis; NO known hypersensitivity to NAC, NO history of life threatening contrast reaction
Jo, 2008[51]	2	RCT/ Controlled trial	Yes	NR	NR	Multi-center	>19years; Coronary angiography; Creatinine clearance rates <60ml/min, Baseline SrCr >1.1mg/dl, no pregnancy, no lactation, no prior contrast media administration within 7 days of study entry, no emergent coronary angiography, no acute renal failure, no end-stage renal disease requiring dialysis, no history of hypersensitivity reaction to contrast media, no cardiogenic shock, no pulmonary edema, no multiple myeloma, no mechanical ventilation, no parenteral use of diuretics, no use of NAC or ascorbic acid, and use of metformin or nonsteroidal anti-inflammatory drugs within 48 hrs of the procedure no recent statin users (within 30 days before the procedure)

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Jo, 2009[52]	2	RCT/Controlled	Yes	2005 to 2006	NR	Multi-center	Age ≥19 years of age; CrCl ≤60 ml/min or SrCr ≥1.1 mg/dl; Undergoing coronary angiography; Not pregnant; Not lactating; No history of hypersensitivity reaction to contrast media; No cardiogenic shock, pulmonary edema or emergent coronary angiography; No acute renal failure or end stage renal disease requiring dialysis; No prior contrast media administration within 7 days of enrollment; No multiple myeloma or mechanical ventilation; No parenteral use of diuretics; No use of NAC or ascorbic acid; No use of metformin or nonsteroidal anti-inflammatory drugs within 48 hours of procedure.
Jo, 2014[53]	2	RCT/ Controlled	Yes	2007 to 2009	NR	Multi-center	Patients with STEMI; Undergoing PCI; No cardiogenic shock; No need for intravenous vasopressors or intra-aortic balloon pump; No previous MI; Not a current statin user
Kama, 2014[54]	1,2	RCT/ Controlled	Yes	NR	Inpatient (including ICU)	Single-center	Age ≥18 years; presented at the emergency department in 2011; received contrast-enhanced CT; moderate or high risk according to Mehran CIN risk score (>5 points); no history of contrast-related allergies; hemodynamically staqble without requiring excessive fluid resuscitation or surgery; not receiving renal replacement therapy; provided informed consent form.
Katoh, 2014[55]	2	Non-RCT	Yes	2010 to 2011	NR	Single-center	Undergoing CAG or PCI; eGFR <45 ml/min/1.73m^2; No acute coronary syndrome, no cardiogenic shock, no congestive heart failure, no pregnancy, no dehydration, no intravascular administration of contrast medium within the previous 7 days, no chronic dialysis, and no history of allergy to the contrast medium (Iopamidol).
Kay, 2003[57]	2	RCT/ Controlled	No	2006 to 2008	NR	Single-center	>21years estimated GFR between 30 and 60mlmin/1.73m^2 Patients with NO acute coronary syndrome, cardiogenic shock, chronic hemodialysis treatment, overt congestive heart failure, recent exposure to radio-contrast medium within preceding 14 days, emergent procedure. Patients NOT pregnant, patients with NO known allergy to NAC, theophylline or to contrast agents, contraindications to theophylline (history of seizures, arrhythmia resulting in haemodynamic instability and/or Lown classification (5A)or higher within 24 h before administration of contrast medium) and patients who were NOT taking any medication that has been shown exerting pharmacokinetic interaction with theophylline [cimetidine, isoproterenol (intravenous), salbutamol, terbutaline, corticosteroids, macrolide antibiotics, fluoroquinolones, rifampicin, isoniazid, phenytoin, carbamazepine, barbiturates, antacids (magnesium/aluminium hydroxide)]
Kaya, 2013[56]	2	RCT/ Controlled	Yes	2011 to 2011	NR	Single-center	Undergiong primary PCI; diagnosed with STEMI; No known hypersensitivity to contrast agents and statins; creatinine clearance >60ml//min; No chronic renal failure requiring dialysis; No cardiogenic shock manifestations; No pregnant and lactating females; No previous statin use; No patients who had received a contrast agent for any reason with the last week.
Kefer, 2003[58]	2	RCT/ Controlled	No	NR	NR	NR	Undergoing coronary angiography or PCI; No renal dysfunction, Patients with SrCr concentration < 3mg/dl.
Khalili, 2006[59]	1,2	RCT/ Controlled	No	NR	NR	NR	SrCr concentration above 1.2 mg/dl or creatinine clearance of less than 60 ml/min, Stable SrCr, no acute renal failure, not treated with theophylline, calcium channel blockers, dopamine receptor agonists or diuretics.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Kim, 2010[60]	2	RCT/ Controlled	Yes	NR	NR	Multi-center	>18years; coronary angiography; SrCr values: >1.5 mg/dl (132.6 umol/l) and =<3.0 mg/dl (265.2 umol/l),not pregnant, not lactating, left ventricular ejection fraction >20%, no hemodynamic instability, no acute MI, no planned staged interventional procedures, no participation in investigational drug study within 30 days, no severe liver disease, no allergy to iodinated CM, no jaundice or hematological disease, no scheduled renal angiography, no planned exposure to CM within 72 hrs, no intravascular admin of CM within previous 5 days, ability to return to lab at 48 and 72 hrs, no current intake of nephrotoxic drugs, no acute deterioration or fluctuation of renal function
Kimmel, 2008[61]	2	RCT/ Controlled	No	2005 to 2006	NR	Single-center	>18years, coronary angiography with or without PCI, not on dialysis; no acute renal failure or ESRD, no participation in an investigational drug or device trial within 30 days; not having received CM within 7 days of study entry; not scheduled major surgical intervention; no history of hypersensitivity reaction to iodinated CM; unstable hemodynamic conditions; use of N-acetylcysteine (NAC), metformin, or non-steroidal anti-inflammatory drugs within 48 hour to the procedure; intravenous use of diuretics or mannitol; and pregnancy or lactation. CrCl <60ml/min
Kinbara, 2010[62]	2	RCT/ Controlled trial	No	2006 to 2007	Inpatient (including ICU)	Single-center	Coronary angiography; Other Risk factors, Stable coronary artery disease; Exclusion criteria of this study included acute myocardial infarction requiring primary or rescue PCI, use of vasopressors before PCI, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis, or allergies to the medications being studied
Koc, 2012[63]	2	RCT/ Controlled trial	No	NR	NR	Multi-center	>18yrs of age; undergoing coronary angiography and/or PCI; mild to moderate renal dysfunction with serum creatinine (SCr) > 1.1 mg/dL or creatinine clearance < 60 mL/min; Does not have contrast-agent hypersensitivity, pregnancy-lactation, decompensated heart failure, pulmonary edema, emergency catheterization, acute renal failure or end-stage renal failure
Koc, 2013[64]	2	RCT/ Controlled	No	2009 to 2010	NR	Multi-center	>18 years, undergoing coronary angiography or PCI; T2DM; use of oral hypoglycemic agents or insulin, fasting plasma glucose levels greater than 126 mg/dL, or a random plasma glucose level of 200 mg/dL or greater, No contrast-agent hypersensitivity, pregnancy lactation, decompensated heart failure, pulmonary edema or severe renal impairment (defined as SrCr [SCr] >3.0 mg/dL), emergency procedures. No previous contrast agent administration within 7 days of study enrollment.
Kooiman, 2014[65]	1	RCT/ Controlled	Yes	2010 to 2012	Inpatient (including ICU) and Outpatient	Multi-center	Age >18; Undergoing CT; eGFR <60 ml/min/1.73 m^2; not pregnant, no previous contrast administration within last 7 days; no allergy to iodinated contrast meida; no haemodynamic instability; no previous participation in the trial.
Kotlyar, 2005[66]	2	RCT/ Controlled	No	NR	NR	Single-center	Elective coronary angiography and/or coronary intervention; no acute coronary syndrome requiring emergent coronary angiography or primary coronary intervention, no cardiogenic shock, no iodinated contrast media administration within a month or N -acetylcysteine within 48 h before the study entry, no current dialysis or a SrCr concentration N 1.4 mg/dL for men, or N 1.2 mg/ dL for women, no thyroid diseases, or no allergy to the study medication. Normal renal function (SrCr <1.4 mg/dl in men and <1.2 mg/dl in women)

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Kumar, 2014[67]	2	RCT	Yes	NR	Inpatient (including ICU)	Single-center	All patients willing to undergo angiography and angioplasty with or without risk factors and patients who received maximum or less than maximum permissible dose of the dye calculated from 5x bodyweight (kg)/ serum creatinine in mg%. No patients who were and continuing on any nephrotoxic drugs, no patients already suffering from gout or serum uric acid levels >10mg/dl, no previous hypersensitivity or intolerance to allopurinol, no congestive heart failure or ejection fraction < 40% and ability to give consent.
Lawlor, 2007[68]	2	RCT/ Controlled	No	NR	Outpatient	Single-center	Undergoing angiography for peripheral vascular disease and aneursymal disease; stable chronic renal impairment; Patients with serum creatinine concentrations greater than 140 mmol/L or estimated creatinine clearance < 50 mL/min were eligible.patients with stable, chronic renal insufficiency patients with hemodynamic stability, those who no medical reasons to not tolerate the hydration protocol, No known sensitivity to NAC (gastrointestinal intolerance, urticaria), and those able to provide informed consent
Lee, 2011[69]	2	RCT/ Controlled	Yes	2008 to 2009	NR	Multi-center	> 18years, coronary angiography; T2DM; Diagnosed with diabetes mellitus; SrCr >1.1 mg/dl but <9mg/dl. eGFR <60 ml/min/1.73m^2, but >15 ml/min/1.73m^2, Other Risk factors, No end stage renal disease on hemodialysis. No multiple myeloma, pulmonary edema or uncontrolled blood pressure. No acute ST-segment elevation myocardial infarction, emergency coronary angioplasty/angiography, contrast media within previous 2 days, pregnancy or allergies to contrast media/medications.
Lehnert, 1998[70]	1,2	RCT/ Controlled	No	NR	NR	Single-center	Angiography with at least 1.2 ml/kg/BW contrast medium dose (specific type of test was not listed as inclusion criterion); All patients with stable SrCr of at least 1.4mg/dl undergoing angiography with contrast medium dose of greater than or equal to 1.2ml/kg BW, non-pregnant women, no known allergy to contrast medium, no prior exposure to contrast medium in past 14 days before the start of the protocol, and no diagnosis of end-stage renal disease
Leoncini, 2014[71]	2	RCT/ Controlled	No	2010 to 2012	Inpatient (including ICU)	Single-center	Undergoing non emergent coronary angiography; have acute coronary syndrome; No current statin treatment; No high-risk features warranting emergency coronary angiography (within 2 h); No acute renal failure or end-stage renal failure requiring dialysis, or serum creatinine ≥3 mg/dl; No severe comorbidities which precluded early invasive strategy; No contraindications to statin treatment; No contrast medium administration within the previous 10 days; No pregnancy; No refusal of consent
Li, 2012[72]	2	RCT/ Controlled	No	2009 to 2011	Emergency department	Single-center	PCI; not on dialysis, ; Other Risk factors, acute STEMI, not on current or previous (<3 months) statin treatment, no history of renal and hepatic dysfunction, no prior fibrinolysis, unconsciousness at arrival, cardiogenic shock with intraaortic balloon pumping, uncontrolled hypertension (blood pressure >200/120 mm Hg) or stroke, a recent major operation (<3 months) or refusal to receive emergency PCI

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Li, 2014[73]	2	RCT/ Controlled	No	2010 to 2010	Inpatient (including ICU)	Single-center	Undergoing CAG or PCI for coronary heart disease; No alanine transaminase ≥80 U/L; No serum creatinine > 264 μmol/L; No cancer patients, blood diseases or autoimmune diseases; No cardiogenic shock, and left ventricular ejection fraction ≤30%; No gout; No history of hypersensitivity to contrast media; No atorvastatin or probucol; No prolonged QT interval (corrected QT interval > 0.44 s); No previous contrast media exposure within 7 days of study entry; No pregnancy, or lactation; No patients who had used diuretics during hospitalization or used probenecid, benzbromarone, or allopurinol; No patients who had used statins or probucol within 30 days or had used *N*acetylcysteine or nonsteroidal anti-inflammatory drugs.
Liu, 2014[74]	2	Prospective		2010-2012	Inpatient	Single	patients with an estimated glomerular filtration rate (eGFR) of 30–90 mL/min/1.73 m2 (CKD stages II and III), and patients pretreated with either atorvastatin (20 mg) or rosuvastatin (10 mg), at equivalent standard doses [16]. Statin pretreatment was defined as taking a statin 2–3 days before CM exposure and 2–3 days after the procedure. Patients were excluded if they had undergone chronic statin therapy (.14 days); had been treated with simvastatin or other statins; had a history of heart failure (defined as NYHA III/ IV or Killip class II–IV), pregnancy, CM allergy, CM exposure during the previous 7 days; or had been treated with potentially nephroprotective (e.g., N-acetylcysteine or theophylline) or nephrotoxic (e.g., steroids, non-steroidal anti-inflammatory drugs, aminoglycosides, amphotericin B) drugs [17]. No patients with CKD stages 0, IV or V; hepatic insufficiency; or who had undergone renal transplantation or dialysis.
MacNeill, 2003[75]	2	RCT/ Controlled	No	NR	NR	NR	Elective cardiac catheterization; SrCr greater or equal to 1.5 mg/dl on the morning of the planned procedure, Without Acute renal failure, without dialysis dependent chronic renal failure diagnosis, no exposure to contrast within the preceding 5 days, no pregnant women, no known sensitivity to NAC (no emergent procedures; the diagnostic test procedure is already labeled as "elective")
Manari, 2014[76]	2	RCT/ Controlled	No	2007 to 2010	Inpatient (including ICU)	Multi-center	>18 years of age; undergoing PCI; has a STEMI; chest pain for at least 30 min with ST=segment elevation of 0.2mV or morein at least 2 contiguous leads or new left bundle branch block; no mechanical complications; no previous peritoneal or hemodialysis treatment; no postanoxic coma; not pregnant.
Marenzi, 2006[78]	2	RCT/ Controlled	No	2003 to 2005	Inpatient (including ICU) other	Single-center	Primary angioplasty; Other Risk factors, AMI, Presented within 12 hrs (18hrs in cases of cardiogenic shock) after the onset of symptoms. Absence of long-term dialysis and known allergy to N-acetylcysteine.
Marenzi, 2003[77]	2	RCT/ Controlled trial	No	NR	Inpatient (including ICU)	Single-center	coronary angiography or elective percutaneous coronary intervention; chronic renal failure; SrCr > 2mg/dl and creatinine clearance < 50 mL/min; no acute coronary syndrome; no cardiogenic shock; no long-term peritoneal dialysis or HD treatment; no overt CHF; no recent major bleeds; no contraindications for anticoagulant therapy.Enrolled patients with CRF who were scheduled for coronary angiography or an elective percutaneous coronary intervention at their institution.

Masuda, 2007[80]	2	RCT/ Controlled trial	No	2005 to 2006	Inpatient (including ICU)	Single-center	>20 years; Coronary angiography; SrCr greater than 1.1mg/dl or estimated glomerular filtration rate less than 60ml/min; no change in SrCr concentration of >/=0.5 mg/dl during the previous 24 hrs, no preexisting dialysis, no recent exposure to radiographic contrast media within 2 days of the study, no allergy to radiographic contrast media, no pregnancy, no previous or planned administration of mannitol, fenoldopam, N-acetylcysteine or nonstudy NaHCO3

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Matejka, 2010[81]	2	RCT/ Controlled	No	2005 to 2008	Inpatient (including ICU) Outpatient	Single-center	>18years, coronary angiography or percutaneous coronary intervention,; Cr >/= 1.47mg/dl, Exclusion criteria were long-term dialysis, pregnancy, lactation, epilepsy, thyrotoxicosis, theophylline allergy, previous theophylline medication, arrhythmias with hemodynamic instability, severe liver dysfunction, clinical signs of dehydration and inability to take oral fluids. Use of angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs and other concomitant medications was left to the attending physician's discretion.
Miner, 2004[83]	2	RCT/ Controlled	No	NR	NR	Single-center	PCI or coronary angiography; Patients without diabetes with a calculated creatinine clearance (Cockcroft-Gault formula) <50 mL/min. Patients with diabetes were eligible if their calculated creatinine clearance was <100 mL/min. Any patient with an absolute SrCr >200 mol/L was eligible. Absence of renal replacement therapy (dialysis or transplantation, reactive airway disease requiring oral steroids, baseline systolic blood pressure <80 mm Hg. Absence of active congestive heart failure; No acute myocardial infarction (defined as ongoing chest pain with electrocardiographic changes); Not enrolled in another clinical trial; ability to provide informed consent; NO ongoing need for intravenous nitroglycerin; NO treatment with NAC within 72 hrs of planned PCI. Women not of childbearing age.
Motohiro, 2011[84]	2	RCT/ Controlled trial	No	2004 to 2007	Inpatient (including ICU)	Multi-center	>20years; coronary angiography; GFR <60 AND Cr < 4
Ochoa, 2004[85]	2	RCT/ Controlled	No	NR	NR	Single-center	Elective or urgent coronary angiography and/or PCI; chronic renal insufficiency (SrCr >1.8 mg/dL (males), >1.6 mg/dL (females), or a calculated creatinine clearance <50 mL/min (Cockcroft-Gault formula, No recent (<6 weeks) elevation in SrCr >0.5 mg/dL, Not actively receiving any form of renal dialysis or dialysis planned post-angiography, No prior contrast media exposure within 48 hrs, No known allergy to N-acetylcysteine or history of anaphylaxis to intravenous contrast media, No recent decompensated congestive heart failure (<4 weeks) No cardiogenic shock or use of intravenous vasopressors within 1 week, No known or suspected severe aortic valve stenosis (area <1.0 m2, mean gradient >50 mmHg), and No recent (<4 weeks) initiation of diuretics or ACE inhibitors
Oldemeyer, 2003[86]	2	RCT/ Controlled	No	NR	NR	NR	>18 years and <80 years, Angiography history of chronic renal failure, stable SrCr concentrations >1.4 and <5.0mg/dl. No acute myocardial infarction, ARF, renovascular hypertension, prior vasopressor usage, cardiogenic shock and current peritoneal or hemodialysis.
Ozcan, 2007[87]	2	Dec_nRCT	No	NR	NR	NR	Coronary angiography and or percutaneous coronary intervention,; chronic renal insufficiency (mean [±SD] SrCr concentration 2.0±0.39 mg/dl), no patients with acute renal failure, acute myocardial infarction requiring primary or rescue coronary intervention within less than 12 h, cardiogenic shock, current peritoneal or hemodialysis, planned post-contrast dialysis, or a known allergy to acetylcysteine. SrCr >1.5 mg/dl or creatinine clearance of <50 ml/min.
Ozhan, 2010[88]	2	RCT/ Controlled	No	NR	NR	Single-center	Coronary or peripheral angiography and or PCI; CR > 1.5, creatinine clearance <60ml/min

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Patti, 2011[89]	2	RCT/ Controlled	Yes	NR	NR	Multi-center	Undergoing PCI, CVD; unstable angina or non–ST-segment elevation myocardial infarction; Statin naive. No current or recent statin treatment (<3months). No non–ST-segment elevation ACS with high-risk features warranting emergency coronary angiography (<2 hrs), no any baseline increase in liver enzymes (aspartate aminotransferases/alanine aminotransferases), left ventricular ejection fraction >30%, renal failure with a creatinine level <3 mg/dl, and no history of liver or muscle disease.
Poletti, 2007[90]	1	RCT/ Controlled	No	NR	NR	NR	>19years, cath +/- PCI ; Cr >1.2 - CrCl<50ml/min, No acute kidney failure, were undergoing dialysis, or had unstable renal function as evidenced by a change in SrCr of 0.5 mg/dL or 25% in the prior 10 days. No known allergy to contrast or acetylcysteine, administration of mannitol, intravenous catecholamines, parenteral diuretics, theophylline, or a contrast agent within 7 days of study entry. No mechanical ventilation, cardiogenic shock, or emergent angiography.
Qiao, 2015[91]	2	RCT/ controlled		2009-2009	Inpatient	NS	No pregnancy, lactation, Ketoacidosis, Lactic acidosis, prior CM administration within 7 days of study entry, emergent coronary angiography, history of hypersensitivity reaction to CM and statins, New York Heart Association class IV congestive heart failure, unstable renal function, and use of aminophylline or prostaglandin E1 within 7 days of the procedure. Importantly, all patients who were recent statin users (with 14 days before the procedure) were excluded. This study was approved by the institutional review board at our institution.
Quintavalle, 2012[92]	2	RCT/ Controlled	Yes	2005 to 2008	NR	NR	Undergoing coronary angiography, or PCI; eGFR < 60 ml/min/1.73m^2 enrolled in the Novel Approaches for Preventing or Limiting Events (NAPLES) II trial
Rashid, 2004[94]	2	RCT/ Controlled	Yes	NR	NR	Single-center	Patients with peripheral vascular disease; Undergoing elective angiography or angioplasty
Ratcliffe, 2009[93]	2	RCT/ Controlled	No	2007 to 2008	Inpatient (including ICU) Outpatient	Single-center	coronary angiography or coronary angioplasty; elevated SrCr (greater than 132.6 µmol/L in men, and greater than 114.9 µmol/L in women) or reduced calculated creatinine clearance (less than 1.002 mL/s) using the Cockcroft-Gault formula, Other Risk factors, DM on oral antiglycemic or insulin therapy, no acute MI, no Signs of heart failure or EF <35%, no cardiogenic shock, no hypertrophic or restriction cardiomyopathy, no contrast media exposure in last week, no previous reaction to contrast media, no renal transplantation, no dialysis, no severe comorbid illness, no use of dopamine, mannitol, or fenoldopam, no newly diagnosed uncontrolled DM, no inability to follow-up
Reinecke, 2007[95]	2	RCT/ Controlled	No	2001 to 2004	Inpatient (including ICU)	Single-center	Elective coronary angiography; SrCr concentrations ≥1.3 mg/dl and ≤3.5 mg/dl. Absence of acute or recent (within 30 days) myocardial infarction, congestive heart failure (New York Heart Association class IV), recipient of transplanted organs,monoclonal gammopathy, and/or previous contrast medium administration within 7 days
Sadat, 2011[96]	2	RCT/ Controlled	No	NR	NR	Single-center	Angiography +/- PCI,CVD; EF>35; ; Cr>1.2, creatinine clearance <60ml/min, No dialysis, acute renal failure, change in use of diuretic or antihypertensive agents or who had received contrast media within 30 days of entry. No congestive heart failure or severe valvular disease. No advanced left ventricular systolic dysfunction. Left ventricular ejection fraction >35%. No chronic lung disease or asthma exacerbation or allergy to acetylcysteine.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Sandhu, 2006[97]	2	RCT/ Controlled	No	2001 to 2002	Outpatient	NR	Renal-mesenteric or aortic angiography (noncoronary angiography);
Sanei, 2014[98]	2	RCT/ controlled		2013-2014	Inpatient	Single	No unstable angina, myocardial infarction, cardiac arrhythmias, heart failure, acute or chronic renal failure, serum creatinine level > 1.5 mg/dl, intravascular administration of contrast material in the past month, known hypersensitivity to statins, and those who were living out of the city and were not able to refer for the follow-up evaluation.
Sar, 2010[99]	1	RCT/ Controlled	No	NR	NR	NR	Undergoing CT: Serum creatinine level >1.2 mg/dl; no Body mass index lower than 21 or greater than 30 kg/m 2 ; no Patients with concomitant systemic diseases, i.e., heart failure, substantial edema, uncontrolled hypertension, hypoalbuminemia (serum albumin level <3.5 g/dL), or ascites due to chronic liver disease;no Patients who have had any nephrotoxic agents (i.e., non- steroidal anti-inflammatory drugs, aminoglycoside or intravenous contrast agent) or drugs affecting the renin angiotensin aldosterone system within the last 30 days; no Patients who had allergic hypersensitivity or other vasoactive reactions to the contrast agents
Seyon, 2007[100]	2	RCT/ Controlled trial	No	NR	Inpatient (including ICU)	NS	>18yrs; coronary angiography; , baseline creatinine equal to or greater than 125 mol/L (1.4 mg/dL) for males or equal to or greater than 115 mol/L (1.3 mg/dL) for females; ACS, baseline SrCr 1.4 mg/dl (males) 1.3 mg/dl (females) or greater; no hemodynamic instability; not pregnant; no acute GI disorders; Killip class > III; NYHS < III; suitable to receive IV hydration; not sensitive to NAC; not receiving theophylline or manitol; not on dialysis; not in another study or using an experimental drug.
Shavit, 2009[101]	2	Non-RCT	No	2004 to 2007	NR	Single-center	>18 years; no preexisting dialysis, patients with CKD stage III–IV (eGFR 15–60mL/min), Patients with plasma creatinine levels more than 8 mg/dL or eGFR less than 15 mL/min, change in plasma creatinine levels of ≥0.5 mg/dL during the previous 24 hrs, multiple myeloma, pulmonary edema, uncontrolled hypertension (systolic>160 mmHg, diastolic >100 mmHg), recent exposure to radiographic contrast, or other nephrotoxic medications(within 2 days of the study), allergy to radio-contrast, or pregnancy were excluded.
Shehata, 2015[102]	2	RCT/ controlled		2012-2014	Inpatient	Single	No severe CKD (e GFR <30 mL/min/1.73 m) [9], end-stage renal disease (or patients on hemodialysis), intake of potentially nephrotoxic drugs (e.g., Nonsteroidal anti-inflammatory drugs and furosemide), acute myocardial infarction requiring emergency coronary intervention, cardiogenic shock, prior history of acute coronary syndrome, prior history of PCI or coronary artery bypass graft surgery, congenital heart disease or any myocardial disease apart from ischemia, known skeletal muscle disorder or chronic liver disease, limited life expectancy due to coexistent disease, for example malignancy, contraindications for aspirin and/or clopidogrel use.

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Shyu, 2002[104]	2	RCT/ Controlled	No	NR	NR	NR	Scheduled for cardiac angiography, serum creatinine concentrations 2.0 mg/dl and 6.0 mg/dl or rates of CrCl 40 ml/min and 8 ml/min, Other Risk factors, Stable creatinine levels: A difference of <0.1 mg/dl between baseline and follow-up at 2 weeks after procedure, Included if patient does not have acute myocardial infarction requiring primary or rescue coronary intervention, use of vasopressors before procedure, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis or allergies to the study medications.
Spargias, 2004[103]	2	RCT/Controlle d	Yes	NR	NR	Single-center	Undergoing nonemergent coronary angiography; Serum creatinine ≥1.2 mg/dl within 3 months of planned procedure; No known acute renal failure; No end stage renal disease requiring dialysis; No intravascular administration of contrast medium within the previous 6 days; No anticipated readministration of contrast medium within the following 6 days; No use of vitamin C supplements on a daily basis during week before procedure; ability to administer the study medication at least 2 hours before procedure.
Tanaka, 2011[105]	2	RCT/ Controlled trial	No	2007 to 2008	Inpatient (including ICU)	Single-center	Coronary angiogram
Tepel, 2000[106]	1	RCT/ Controlled	No	NR	NR	NR	history of chronic renal failure and with stable SrCr concentrations,No patient with acute renal failure was included
Thayssen, 2014[107]	2	RCT/ Controlled	No	2010 to 2012	Inpatient (including ICU)	Multi-center	Age >18 years; undergoing PCI; has STEMI; No cardiogenic shock; being conscious; No ventricular fibrillation or cardiac arrest before primary PCI; No malignant disease, severe infection, or chronic treatment with dialysis; No cardiac surgery or any other major surgery within 30 days after index PCI; No new contrast media examination (ie, CAG or PCI) within 30 days.
Thiele, 2010[108]	2	RCT/ Controlled	Yes	2000 to NR	NR	Single-center	coronary angiography +/- PCI; Cr >1.2 ,creatinine clearance <70ml.min
Toso, 2010[109]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	Computer tomography (CT) or digital subtraction- A total of 80 patients were enrolled. Forty patients tion angiography; creatinine >1.5mg/dl, supposed to receive at least 80 ml of a low-osmolality CM (iopromide) during procedure, no history of allergic reactions to CM or theophylline, no pregnancy, no uncontrolled arterial hypertension, no severe heart failure, no liver failure and no nephrotic syndrome

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Traub, 2013[110]	1	RCT/ Controlled	No	NR	Emergency department	Multi-center	>18 years; undergoing emergency chest-abdome or pelvis CT; willing to provide written consent; no end-stage renal disease undergoing regular peritoneal or hemodialysis; not pregnant; no known allergy to NAC;clinically stable; no currently being treated with NAC; Must have one of the following conditions: preexisting renal dysfunction, diabetes mellitus, hypertension, coronary artery disease, use of nephrotoxic drugs, liver disease, congestive heart failure, >65 years of age, or anemia.
Ueda, 2011[111]	2	RCT/ Controlled trial	No	2008 to 2010	Emergency department	Single-center	>20years; coronary angiography or PCI; no SrCr change >/= 0.5 mg.dl within 24 hrs of procedure; no dialysis; no CM exposure 2 days prior to procedure; no CM allergy; not pregnant; no planned administration of mannitol, fenoldopam, NAC, theophylline, dopamine, or non-study sodium bicarb.
Vasheghani-Farahani, 2010[112]	2	RCT/ Controlled	No	2007 to 2008	Inpatient (including ICU)	Single-center	>18years coronary angiography,; SCr > 1.5, Uncontrolled hypertension CHF NYHA III-IV no unstable SrCr (change in creatinine concentration of at least 0.5 mg/dL or 25% from creatinine measured prior to the study to that of the day of angiography [baseline creatinine]); no previous history of dialysis; no eGFR <20 ml/min per 1.73 m 2 (calculated with the 4-variable Modification of Diet and Renal Disease Study equation) (15); no emergency catheterization; no recent exposure to radiographic contrast agents (within 2 days prior to the study); no allergy to contrast agent; no pregnancy; no administration of dopamine, mannitol, fenoldopam or N-acetylcysteine during the intended time of the study; no need for continuous hydration therapy (e.g., sepsis); and no multiple myeloma
Vogt, 2001[113]	1, 2	RCT/ Controlled trial	No	NR	Inpatient (including ICU)NR	Single-center	transluminal renal angioplasty, percutaneous transluminal angioplasty of the lower extremities, coronary angiography, CT, other radiographic investigation; chronic stable renal failure (SrCr > 2.3 mg/dL); Hardly any IC at all
Wang, 2008[114]	2	RCT/ Controlled	No	NR	NR	Single-center	Undergoing coronary angiography; unstable angina; No long-term dialysis, no AMI, no, pulmonary edema, no known allergy to NAC, no recent exposure to radiographic contrast within the preceding two days, and no administration of dopamine, mannitol or fenoldopam.
Webb, 2004[115]	2	RCT/ Controlled	No	NR	NR	Multi-center	Undergoing diagnostic cardiac catheterization or percutaneous coronary intervention; GFR < 50 ml/min, GFR of <50ml/min, no suspected acute renal failure, Creatinine <400umol/l, not currently on dialysis, hemodynamic stability, No NAC administration within 48 hrs, and must be able to give informed consent and comply with follow-up.
Xinwei, 2009[116]	2	RCT/ Controlled trial	No	2007 to 2008	Inpatient (including ICU)	Single-center	Percutaneous Coronary Intervention; Other Risk factors, Acute Coronary Syndrome: ACS was defined as any one of the following: (1) unstable angina pectoris; (2) ST-segment elevation myocardial infarction; and (3) non–ST-segment elevation myocardial infarction; ; The following exclusion criteria were used: pregnancy, lactation, previous contrast media exposure within 7 days of study entry, acute renal failure, end-stage renal disease requiring dialysis, alanine transaminase elevation, history of hypersensitivity to contrast media, multiple myeloma, cardiogenic shock, and left ventricular ejection fraction 40%. Also, patients who had used statins within 30 days were excluded. Patients who had undergone primary PCI or had undergone PCI within 5 days after enrollment were excluded from the present study

Evidence Table E-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria
Yeganehkhah, 2014[117]	2	RCT	Yes	NR	Inpatient (including ICU)	Single-center	The existence of at least one risk factor of contrast-induced nephropathy, including congenital heart failure [ejection fraction (EF) <40%], history of diabetes mellitus, age >65 years, renal failure (eGFR <60 mL/min/1.73m2 or Cr ≥1.5 mg/ dL), and hypertension. No pregnancies and lactation, no history of allergic reaction to contrast agents, no cardiogenic shock, no pulmonary edema, no multiple myeloma, no mechanical ventilation, no urgent coronary angiography, no serum Cr >4 mg/dL, and no end-stage renal disease (ESRD), not receiving contrast agents two days prior to the study and 48 hours within the study or using diuretics, NAC, sodium bicarbonate, theophylline, dopamine, mannitol, fenoldopam, metformin, and non-steroidal antiinflammatory drugs during the study. No uncontrolled and diastolic blood pressure >100 mm Hg) and no need for further fluid therapy, and no hypertension (treated systolic blood pressure >160 mm Hg and diastolic blood pressure >100 mm Hg) and no need to further fluid therapy.
Yun, 2014[118]	2	RCT/ controlled	Yes	2009-2012	Inpatient	NR	No current statin treatment, high-risk features warranting emergency coronary angiography (within 2 hours), acute renal failure or end-stage renal disease requiring dialysis, serum creatinine >3 mg/dL, contrast medium administration within the past 10 days, or lack of laboratory data including serum creatinine.
Zhang, 2015[119]	2	RCT/ controlled		NR	Inpatient	Multiple	No hypersensitivity to contrast medium or statins, type 1 DM, ketoacidosis, lactic acidosis, Stage 0 or 1 CKD, Stage 4 or 5 CKD, acute ST-segment elevation myocardial infarction within the previous 4 weeks, Class IV heart failure (as defined by the New York Heart Association [NYHA] functional classification system), hemodynamic instability, administration of iodinated contrast medium during the 2 weeks before randomization, low-density lipoprotein cholesterol (LDL-C) concentration <1.82 mmol/L, and hepatic dysfunction or renal artery stenosis (unilateral >70% or bilateral >50%).
Zhou, 2012[120]	2	RCT/Controlled	Yes	2008 to 2009	NR	Single-center	Undergoing coronary catheterization; ≥18 years of age; eGFR <60 ml/min/1.73 m^2 or SrCr ≥1.1 mg/dl; No acute renal failure; No end stage renal disease requiring dialysis; No unstable renal function; No uncontrolled diabetes mellitus or hypertation; No New York Heart Association class IV congestive heart failure or left ventricular ejection fraction <35%; No administration of iodinated contrast medium from 7 days before to 72 hours after administration of study agents; No administration of any medication to prevent CIN such as NAC or intake of nephrotoxic medications from 24 hours before to 24 hours after the administration of the study agent; No recent ascorbic acid users (within 30 days before procedure)

ACE= Angiotensin Converting Enzyme, ACEI=Angiotensin Converting Enzyme Inhibitor, ACS=Acute Coronary Syndrome, AMI=Acute Myocardial Infarction, ARB=Angiotensin Receptor Blocker, ARF=Acute Renal Failure, AZ=Acetazolamide, BW=Body Weight, CABG=Coronary Artery Bypass Grafting, CAG= Coronary angiogram, Cc/kg=cubic centimeter per kilogram, CE-MDCT=Contrast Enhanced Multi-detector Computer Tomography, CHF=Chronic Heart Failure, CIN=Contrast Induced Nephropathy, CKD=Chronic Kidney Disease, CM=Contrast Media, Cr=Creatinine, CrCl=Creatinine Clearance, CRF=Chronic Renal Failure, CT=Computer Tomography, CVD=Cardiovascular Disease, EF=Ejection Fraction, eGFR=estimated Glomerular Filtration Rate, ESRD=Endstage Renal Disease, GFR=Glomerular Filtration Rate, GI=Gastrointestinal, H=hour, HD=Hemodialysis, IA=Intrarterial, ICU=Intensive Care Unit, IV=Intravenous, LDL=Low Density Lipoprotein, LVEF=Left Ventricular Ejection Fraction, MDCT=Multi-detector Computer Tomography, MDRD= Modification of Diet in Renal Diseases, mEq/l=milliequivalents per liter, Mg/dl=milligrams per deciliter, mg=milligram, MI=Myocardial Infarction, Ml/min/1.73m^2=milliter per minute per 1.73 meter squared, Ml/min=milliliter per minute, mmHG=millimeter of Mercury, Mol/l=mole per liter, NAC=N-acetylcysteine, NR=Not Reported, NSAID=Non-steroid Inflammatory Drug, NYHA=New York Heart Association, PCI=Percutaneous Coronary Intervention, PCr=Plasma Creatinine, RCT=Randomized Controlled Trial, SrCr=SrCr, STEMI= ST Elevation Myocardial Infarction, T2DM=Type 2 Diabetes Mellitus, Umol/l=micromole/liter, Yrs=years

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Abaci, 2015[1]	Ioversol	IA	Arm 1: 117.7ml Arm 2: 139.2ml	1	IV normal saline	IV		
				2	Risovustatin + IV normal saline	Oral	20mg 2/day (total = 40)	
Acikel, 2010[2]	Iohexol	IA	Average Volume: Arm1: 103ml Arm2: 105ml Arm3: 110ml	1	IV Normal Saline	IV	IV Normal saline 1ml/kg/h 4h prior until 24 after procedure	did not receive any cholesterol lowering medication
				2	IV Normal Saline + Oral Atorvastatin	Oral, IV	40mg/day of oral Atorvastatin, started 3 days before CM admin and continued for 48 hours after.	All participants received IV normal saline 1ml/kg/h 4h prior until 24 after procedure
				3	IV Normal Saline + Chronic Statin Therapy (non-randomized group)	Oral, IV	Received statin therapy for at least 1 month before procedure (non-randomized group). Dose and type of stating not reported	All participants received IV normal saline 1ml/kg/h 4h prior until 24 after procedure
ACT, 2011[3]	LOCM, IOCM, Other description, Also included high-osmolar contrast	IA	Not specified	1	Placebo	Oral	1200mg b.i.d, 4800mg total, 48 hrs, Prior to CM administration After CM administration	2 doses before and 2 doses after procedure. Powdered placebo diluted in water and given orally. Hydration with 0.9% saline, 1 ml/kg per hour, from 6 to 12 hrs before to 6 to 12 hrs after angiography, was strongly recommended
				2	Oral NAC	Oral	1200mg b.i.d, 4800mg total, 48 hrs, Prior to CM administration After CM administration	2 doses before and 2 doses after procedure. Powdered NAC diluted in water and given orally. Hydration with 0.9% saline, 1 ml/kg per hour, from 6 to 12 hrs before to 6 to 12 hrs after angiography, was strongly recommended

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Albabtain, 2013[4]	Ioxaglate	IA	Dose: 320mg of iodine Mean volume: 87.6 (SD 80.4) ml	1	IV Normal Saline	Oral, IV	Standard hydration (not specified)	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.
				2	Oral Ascorbic Acid + IV Normal Saline	Oral, IV	3g oral ascorbic acid, given 2 hours before angiogram, 2 g after angiogram, and 2 g 24 hours after angiogram.	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.
				3	Oral NAC + IV Normal Saline	Oral, IV	600 mg oral NAC twice daily for 2 days, starting evening before procedure.	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.
				4	Oral NAC + Oral Ascorbic Acid + IV Normal Saline	Oral, IV	3g oral ascorbic acid, given 2 hours before angiogram, 2 g after angiogram, and 2 g 24 hours after angiogram. In addition, given 600 mg oral NAC twice daily for 2 days, starting evening before procedure.	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.
Alexopoulos, 2010[5]	Iodixanol, Iomeprol, Iobitridol, Iopentol, Ioxaglate	IA	Average Volume: IOCM: 279 ml (SD 138) LOCM: 259 ml (SD 140)	1	IV Normal Saline + Oral Placebo	Oral, IV	Placebo at least 2 hours before the start of the index procedure, followed by 2 g of placebo the night and the subsequent morning after the procedure.	All participants given 50 to 125 mL/hr intravenous normal saline was started in all patients from randomization until at least 6 hours after the procedure.
				2	IV Normal Saline + Oral Ascorbic Acid	Oral, IV	3 g of ascorbic acid, supplied in chewable tablets, at least 2 hours before the start of the index procedure, followed by 2 g of ascorbic acid the night and the subsequent morning after the procedure.	All participants given 50 to 125 mL/hr intravenous normal saline was started in all patients from randomization until at least 6 hours after the procedure.

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Alioglu, 2013 [6]	Iomeprol	IA	Not specified	1	Control	IV	IV infusion of 1 ml/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to contrast media, Prior to CM administration After CM administration	
				2	NAC	Oral, IV lol	Acetylcysteine 600 mg twice a day, on the day before and on the day of cardiovascular procedure, Prior to CM administration After CM administration	All patients received IV infusion of 1 ml/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to contrast media
Allaqaband, 2002 [7]	LOCM	IA	Mean: Arm1 1.47 ml/kg (SD 0.90), Arm2 1.52ml./kg (SD 0.81), Arm3 1.63ml/kg (SD 0.67), Duration and volume not specified	1	0.45% saline	IV	0.45% Saline: 1 ml/kg/hr, 12 hour before procedure, during procedure, and 12 hrs after procedure, Prior , during CM, and after CM administration	
				2	0.45% saline + NAC	IV	Saline: 1 ml/kg/hr + NAC: 600mg 2x daily, Saline same as Arm 1, NAC: given 12 hrs before and 12 hrs after procedure, Prior to CM, during CM and after CM administration	
				3	0.45% saline + fenoldopam	IV	Saline: 1 ml/kg/hr + Fenoldopam: 0.1 microgram/kg/hr, Saline: same as Arm 1, Fenoldopam: starting 4 hrs before procedure and ending 4 hrs after, Prior to CM, during CM and after CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Amini, 2009[8]	Iodixanol, Iohexol	IA	Not specified	1	Placebo	Oral	NR, 24hrs before and 24hrs after, Prior and After CM administration	The patients were hydrated orally and intravenously. All the patients were encouraged to drink fluids like water and fruit juice for at least 8 glasses over 12 h before the procedure and memorize the number of glasses. The oral preprocedural hydration was estimated by multiplying the number of glasses drunk by 200 ml Patients were hydrated intravenously by 1 L of 0.9 normal saline, which was commenced in the catheterization laboratory
				2	N-acetylcysteine	Oral	600mg b.i.d, 24hrs before and 24hrs after, Prior and After CM administration	
Aslanger, 2012 [9]	Ioxaglate	IA	Not specified, Define, Mean: Arm1 - 204ml, Arm2 - 193ml, Arm3 - 205ml	1	Placebo	IV	12ml saline during procedure, placebo capsules presumably twice daily for 2 days, 48 hrs, During CM administration After CM administration	0.9% saline for 12 hrs at 1 ml/kg/hr
				2	IV NAC	IV	1200mg IV during procedure, 1200mg by mouth twice daily for 2 days, 48 hrs, During CM administration After CM administration	
				3	IA NAC	Other, IA	600mg IA before procedure, 1200mg by mouth twice daily for 2 days, 48 hrs, Prior to CM administration After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Awal, 2011[10]	Not specified,	IA	Not specified	1	IVF Normal saline	IV	1ml/kg 12hrs before and 12hrs after procedure, 12hrs before and 12hrs after procedure, Prior to CM administration After CM administration	
				2	IVF Normal saline+ N acetylcysteine	Oral, IV	600mg NAC twice daily for 2 days plus control group treatment, Starting a day before procedure plus control group treatment, Prior to CM administration After CM administration	
Azmus, 2005 [11]	IA,	NR	Not specified	1	Placebo	Oral	600mg, 72 hrs, Prior to CM administration During CM administration After CM administration	2 doses prior to procedure, 2 doses day of procedure, 1 dose after procedure
				2	NAC	Oral	600mg, 72 hrs, Prior to CM administration During CM administration After CM administration	2 doses prior to procedure, 2 doses day of procedure, 1 dose after procedure
Baker, 2003 [12]	Iodixanol	IA	Not specified, Define, Mean: Arm1 222ml (SD 162), Arm2 238ml (SD 155)	1	Saline only	IV	Saline: 1ml/kg/h, 12 hrs pre-procedure and 12 hrs post-procedure, Prior to CM administration After CM administration	
				2	IV saline + NAC	IV	NAC: 150/mg/kg in 500ml saline, 4.5 hrs, Prior to CM administration After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
BaraNSka-Kosakowska, 2007[14]	LOCM	IA	Mean Volume: Arm 1 :148+/- 58ml Arm 2 :125+/-51ml	1	IV Normal Saline	IV	IV 500ml multielectrolyte fluid beforeprocedure and 500ml 0.9% saline with 20mg IV furosemide after the procedure	
				2	IV NAC + IV Normal Saline	IV	300mg IV NAC before procedure +500ml multielectrolyte fluid before procedure. Then 500ml 0.9% saline with 20mg IV furosemide After procedure	
Baskurt, 2009[13]	LOCM, Ioversol	IA	Not specified	1	Hydration	IV	1 ml /kg/ h for 12 h before and after contrast exposure, 12 h before and after contrast exposure, Prior to CM administration After CM administration	
				2	Hydration + N-acetylcysteine	Oral, IV	1 ml /kg/ h of Isotonic Saline for 12 h before and after contrast exposure + NAC: 600 mg p.o. Twice daily the preceding day and the day of angiography, 12 h before and after contrast exposure, Prior to CM administration	
				3	Hydration + N-acetylcysteine + theophylline	Oral, IV	1 ml /kg/ h of isotonic saline for 12 h before and after contrast exposure.NAC + theophylline (600 mg NAC p.o. And 200 mg theophylline p.o. Twice daily for the preceding day and the day of angiography, 12 h before and after contrast exposure, Prior to CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Beyazal, 2014[15]	Iohexol	IV	30-60	1	0.9% Normal Saline	IV	3 ml/kg 0.9% normal saline 1 hour prior CM and 1ml/kh/hr for 6 hours post CM. Intervention given prior and after CM.	
				2	NaHCO3 + 5% dextrose	IV	150 mEq NaHCO3 in 850ml 5% dextrose, at 3 ml/kg	3 mL/kg for 1 hour before injection of iohexol. After the iohexol injection, 1 mL/kg/h of sodium bicarbonate solution was administered for 6 hours.
				3	0.9% Normal Saline + Diltiazem	Oral, IV	3 ml/kg 0.9% normal saline 1 hour prior CM and 1ml/kh/hr for 6 hours post CM Diltiazem 2x60mg orally, one day prior CM and 2 days post CM	Diltiazem given at at 10:00 and at 22:00.

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Bilasy, 2012 [16]	Iopamidol, LOCM	IA	5 mL × body weight (kg)/SrCr level (mg/dL), Not specified	1	Placebo	IV	100 ml sodium chloride (0.9%) 30 minutes before the procedure, 30 minutes before the procedure, Prior to CM administration	All patients received 0.9% sodium chloride (1 mL/kg per hour) for 24 hours beginning 12 hours before the procedure. The only exception to this were patients with left ventricular ejection fraction (LVEF) <40% or in NYHA III–IV class (New York Heart Association functional class III–IV), where hydration rate was reduced to 0.5 mL/Kg per hour. All patients got NAC 600mg bd for the day before and day of the procedure There is no usual care arm. All patients also got NAC.
				2	Theophylline	IV	200 mg of theophylline in 100 ml NaCl (0.9%) intravenously 30 minutes before CM administration., 30 minutes before the procedure, Prior to CM administration	All patients got NAC 600mg bd for two days
Boccalandro, 2003 [17]	Iodixanol	IA	2.3+/-1.5 mls/kg for control group and 2.3+/-1.7 for acetylcysteine group, Not specified, Define, 191+/-120 mls for control group and 192+/-142 for acetylcysteine group	1	No acetylcysteine+hydration	IV Other, Did not receive acetylcysteine	.45% hallf normal saline 75cc/hr, 12 hrs before and after, Prior to CM administration During CM administration	Both groups had a standardized intravenous hydration regimen with half-normal saline (0.45%) at 75 cc/hr for 12 hr before and after the proce- dure.
				2	Acetylcysteine+hydration	Oral, IV	600mg b.i.d acetylcysteine +.45% hallf normal saline 75cc/hr, day before and the day of the catheterization, Prior to CM administration During CM administration	.45% hallf normal saline 75cc/hr

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Boscheri, 2007[18]	Iodixanol	IA	Mean volume: 106 ml (SD 57)	1	Placebo + IV Normal Saline	Oral, IV	Oral placebo, given as 2 tablets 20 minutes prior to CM.	All participants given 500 ml IV normal saline 2 hours prior and 500 ml normal saline during angiography, and 500 ml normal saline 6 hours after.
				2	Oral Ascorbic Acid + IV Normal Saline	Oral, IV	1 g oral ascorbic acid, given as 2 tablets 20 minutes prior to CM.	All participants given 500 ml IV normal saline 2 hours prior and 500 ml normal saline during angiography, and 500 ml normal saline 6 hours after.
Boucek, 2013 [19]	LOCM	IA or IV	Not specified, Define, Mean: 104ml for NaCl gorup, 115ml for NaHCO3	1	Sodium chloride	IV	154 ml of 8.4% NaHCO3 to 846 mls 5% glucose- 3 ml/kg x 1 hour, then 1 ml/kg/hr, 7 hrs, Prior to CM administration After CM administration	
				2	NaHCO3	IV	154 ml of 5.85% NaCl to 846 ml of 5% glucose-3 ml/kg x 1 hour, then 1 ml/kg/hr, 7 hrs, Prior to CM administration After CM administration	
Brar, 2008[20]	Ioxilan	IA	Not specified	1	NaCl	IV	3ml/kg before and 1.5ml/kg/hr during and after, 1hr before, during and 4hrs after procedure. Prior, during and after cm administration	
				2	NaHCO3	IV	3ml/kg before and 1.5ml/kg/hr during and after, 1hr before, during and 4hrs after procedure. Prior, during and after cm administration	
Briguori, 2002[21]	Iopromide	IA	Not specified	1	Control	NR	Normal saline, NR, Prior to CM administration After CM administration	All patients received saline 0.45% 1ml/kg/h infusion 12 h before-12h after CM
				2	Nac	Oral	NAC 600mg bid 2 days, 2 days, Prior to CM administration After CM administration	The day before and the day of the procedure

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Briguori, 2007[22]	Iodixanol	IA	Dose and duration not specified. Mean volume: Arm 1: 179ml, Arm 2: 169ml, Arm 3: 169ml	1	IV Normal Saline + oral NAC	Oral, IV	IV 0.9% saline, 1ml/kg/hr, 12 hours before and 12 horus after contrast media administration. NAC given at 1200mg twice daily the day before and day after procedure.	All patients given Arm 1 intervention.
				2	IV NaHCO3 + oral NAC	Oral, IV	154mEq/L sodium bicarbonate in dextrose and water. Initial bolus 3ml/kg/hr given 1 hour before contrast media, 1ml/kg/hr during procedure and for 6 horus after.	All patients given Arm 1 intervention, along with sodium bicarbonate.
				3	IV Normal Saline + IV ascorbic acid + oral NAC	Oral, IV	3g of ascorbic acid IV 2 horus before contrast media, and received 2g the night and morning after procedure.	All patients given Arm 1 intervention, along with ascorbic acid.
Brueck, 2013 [23]	LOCM	IA	Not specified, Define, Median contrast volume was 110 mL (IQR, 80-160 mL) in the N-acetylcysteine group, 115 mL (IQR, 90-150 mL) in the ascorbic acid group, and 110 mL (IQR, 80-150 mL) in the placebo group	1	Placebo + IV Normal Saline	IV	Placebo, over the course of 30 minutes, at 24 hrs and 1 hour before applying the contrast material, Prior to CM administration	All patients received 0.9% saline at a rate of 1.0 ml/kg body weight/hour by an infusion pump for 12 hrs prior to and after contrast media administration and continuing for 12 hrs afterward
				2	NAC + IV Normal Saline	IV	600mg, over the course of 30 minutes, at 24 hrs and 1 hour before applying the contrast material, Prior to CM administration	
				3	Ascorbic Acid + IV Normal Saline	IV	500mg, over the course of 30 minutes, at 24 hrs and 1 hour before applying the contrast material, Prior to CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Burns, 2010 [24]	Not specified	NR	Not specified	1	Placebo	IV	Placebo NR, 12 hrs prior to procedure and 12 hrs after, Prior to CM administration After CM administration	All patients received normal saline hydration
				2	Nac	IV	10 g NAC, 12 hrs prior to procedure and 12 hrs after, Prior to CM administration After CM administration	All patients received normal saline hydration
Buyukhatipoglu, 2010[25]	Not specified	NR	Not specified	1	IV Normal Saline	IV	Usual care, IV Normal Saline	
				2	IV NAC + IV Normal Saline	IV	Usual care, IV Normal Saline + 600mg IV NAC	Only one dose given prior to procedure
Carbonell, 2007 [26]	Iopromide	IA	Not specified	1	Placebo	IV Other, placebo	Saline IV for 30 min bid x4doses, 2days, Prior to CM administration After CM administration	Starting 6 hours before CM Saline infusion 6h before-12h after
				2	Nac	IV	NAC 600 mg IV for 30 min bid x4doses, 2days, Prior to CM administration After CM administration	Starting 6 hours before CM
Carbonell, 2010 [27]	Iopromide	IA	Not specified	1	Placebo	IV	Placebo bid, 2 days, Prior to CM administration After CM administration	Saline 0.45% 1ml/kg/h infusion 6h before-12 after
				2	Nac	IV	NAC 600mg bid, 30 min infusion bid - 2 days, Prior to CM administration After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Castini, 2010[28]	Iodixanol	IA	320mg/ml	1	IV normal saline	IV	1 ml/kg isotonic saline body weight per hour for 12 hrs before and 12 hrs after administration of the contrast agent	
				2	Oral NAC + IV normal saline	Oral	600 mg twice daily, NAC, 12 hrs before and 12 hrs after administration of the contrast agent, prior and during CM administration plus IV saline regimen of Arm 1	1 ml/kg body weight per hour for 12 hrs before and 12 hrs after administration of the contrast agent
				3	IV $NaHCO_3$ in 5% dextrose in water	IV	154 ml of 1000 meq/L SB added to 846 ml of 5% dextrose in H_2O. 3 ml/kg for 1 hour immediately before contrast injection. Thereafter, patients received the same fluid at a rate of 1 ml/kg per hour during contrast exposure and for 6 hrs after the procedure. Prior, during and after CM administration	
Chousterman, 2013 [30]	Iohexol	IA and IV	Not specified, Define, 100 mL (90-120) for NAC vs 90mL (80-120) for without NAC	1	Saline	NR	0.9% saline, Prior to CM administration After CM administration	All patients received saline 0.9% 24h infusion- 12 h before and 12 h after examination
				2	Nac	Oral	NAC 2400mg, 2 days, Prior to CM administration After CM administration	37% of the patients received 600mg pre- 63% received 1200mg. All patients received 2400mg total
Chousterman, 2013[30]	Iohexol	Either IA or IV	Median: 90ml in control, 100ml in NAC group	1	No NAC	NR	Nr	All patients received 0.9% saline hydration for 12 hrs before and 12 hrs after procedure.
				2	Nac	Oral	600mg, twice daily, 2400mg total. 48 hrs. Prior and after cm administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Demir, 2008 [31]	Iomeprol, Iopamidol	IV	100ml: Iomeprol (61.25 g/ml) Iopamidol (61.25 g/ml), Not specified, Define, 100ml: Iomeprol (61.25 g/ml) Iopamidol (61.25 g/ml)	1	Saline	IV	2000ml 0.9% saline hydration, 48 hours (24 pre and 24 post), and after CM administration	
				2	Saline + NAC (NAC)	Oral	Hydration as arm 1 + NAC 600 ml/d, 3 days prior, day of, 1 day post procedure	
				3	Saline + Misoprostol (M)	Oral	Hydration as arm 1 + Misoprostol 400 mg/d (200mg, bid), 3 days prior, day of, 1 day post procedure	
				4	Saline + Theophylline (T)	Oral	Hydration as arm 1 + Theophylline 200mg/d, 3 days prior, day of, 1 day post procedure	
				5	Saline + Nifedipine control (N)		Hydration as arm 1 + Nifedipine 30 mg/day, 3 days prior, day of, 1 day post procedure	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Durham, 2002[32]	Iohexol	IA	Mean: Arm1 48.1 min (SD 30.9), Arm2 44.8 min (SD 19.1), Define, Mean: Arm1 84.7 ml, Arm2 77.4 ml	1	IV hydration plus placebo	Oral	Saline 0.45% 1 ml/kg/h, placebo NR, 1h before and 3h after, Prior to CM administration After CM administration	Saline hydration given for 12 hrs before and and up to 12 hrs after procedure All patients were placed on conventional iv hydration but actual rate and duration was left to physician
				2	IV hydration plus NAC	Oral	Saline 0.45% 1 ml/kg/h, 1200mg NAC, 1h before and 3h after, Prior to CM administration After CM administration	Saline hydration given for 12 hrs before and and up to 12 hrs after procedure
Dvorsak, 2013[33]	Iopamidol	IA	Mean Volume Arm1: 130.6 ml Arm2: 144.6 ml	1	IV Normal Saline + placebo	Oral, IV	Placebo given orally before procedure and after procedure in the evening and the next morning	All participants given 50-100ml/h IV normal saline for 2 hours before procedure and 6 hours after
				2	IV Normal Saline + ascorbic acid	Oral, IV	3 g ascorbic acid orally before procedure and 2 g after procedure in the evening and the next morning.	All participants given 50-100ml/h IV normal saline for 2 hours before procedure and 6 hours after
Erturk, 2014[34]	Iopromide	IA	Not specified	1	IV normal saline	IV	Normal saline 1mg/kg/hr, 12 hr prior to and 12 hr after procedure, prior and after CM administration	
				2	Oral NAC + IV normal saline	Oral	Oral NAC 1200 mg (single dose), for twice daily for 24 hr prior to and 48 hr post procedure	Also received IV Normal saline 1mg/kg/hr, 12 hr prior to and 12 hr (Arm 1 regimen)
				3	IV NAC + IV normal saline	IV	IV NAC 2400 mg pre/4800 mg post, within 1 hour prior to procedure and within 4-6 hours after the procedure	Also received IV Normal saline 1mg/kg/hr, 12 hr prior to and 12 hr (Arm 1 regimen)
Ferrario, 2009 [35]	Iodixanol	IA	250 mOsm/kg, Not specified	1	Placebo	Oral, IV	NR glucose placebo pills, 2 days, Prior to CM administration During CM administration	IV 0.9% saline given day before procedure and 24 hrs after procedure
				2	Nac	Oral, IV	600mg NAC twice a day, 2 days, Prior to CM administration During CM administration	IV 0.9% saline given day before procedure and 24 hrs after procedure

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Frank, 2003[36]	Iomeprol	IA	mean dose was 80 mL; 3 CM injections into LCA and 2 injections into the RCA + biplane levocardiography using 25 mL	1	0.9% saline volume expansion	IV	1000 ml 0.9% saline, 12 hrs. Prior and After CM administration	6 hrs pre and 6 hrs post CM admin
				2	0.9% saline voume expansion + high-flux HD	IV + HD	1000 ml 0.9% saline (same as control)HD high flux started 10 min before CM and continued for 4 hrs during CM admin.	
Fung, 2004 [37]	Iopromide, LOCM, Other description, (iodine, 300 mg/mL; Ultavist; Shering Moldova, Berlin, Germany). Note that only iopromide was used. It is a LOCM, but was the ONLY one used	IA	(iodine, 300 mg/mL), Not specified, Define, Arm 1 mean 121.0 +/- 66.2 mL. Arm 2 mean=135.8 +/- 66.6 mL	1	IV hydration+ No drug	IV	Normal saline at 100 ml/h from 12 hrs before the procedure until 12 hrs after the procedure, unless the patient was in clinical heart failure, 24, Prior to CM administration During CM administration After CM administration	Six patients in NAC and 7 patients in the control group could not complete the saline infusion regimen because of clinical heart failure
				2	IV hydration +NAC	Oral, IV	Oral NAC 400 mg, thrice daily the day before and day of the contrast procedure+ normal saline (at 100 ml/h from 12 hrs before the procedure until 12 hrs after the procedure, unless the patient was in clinical heart failure, NAC x 2 days and NS x 24 hrs, Prior to CM administration After CM administration Other, The NS was also given during CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Goldenberg, 2004[38]	Iopamidol	IA	Boluses of 8-15ml, Not specified, Define, boluses of 8-15ml	1	Placebo plus IV saline 0.45%	Oral	N/A, Prior to CM administration During CM administration After CM administration	All patients were treated with IV saline (0.45%) at a rate of 1 ml/kg of body weight per hour for 12 h before and 12 h after administration of the contrast agent. All patients were treated with IV saline (0.45%) at a rate of 1 ml/kg of body weight per hour for 12 h before and 12 h after administration of the contrast agent.
				2	Acetylcysteine plus IV saline 0.45%	Oral	600mg thrice daily, 48hrs, Prior to CM administration During CM administration After CM administration	All patients were treated with IV saline (0.45%) at a rate of 1 ml/kg of body weight per hour for 12 h before and 12 h after administration of the contrast agent.
Gomes, 2005 [39]	Ioxaglate	IA	Not specified, Define, 102.5 (SD 47.3) ml in NAC group; 102.8 (60.4) ml in placebo group	1	Placebo	Oral	Placebo, starting one day before the procedure (two doses before and two doses after the procedure, Prior to CM administration After CM administration	All patients received IV saline 0.9% 1 ml/kg/h from 12 hours before to 12 hours after exposure to the contrast medium All patients received IV saline 0.9% 1 ml/kg/h from 12 hours before to 12 hours after exposure to the contrast medium
				2	N-acetylcysteine	Oral	600mg bid, starting one day before the procedure (two doses before and two doses after the procedure, Prior to CM administration After CM administration	All patients received IV saline 0.9% 1 ml/kg/h from 12 hours before to 12 hours after exposure to the contrast medium

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Gomes, 2012 [40]	Ioxaglate	IA	Not specified, Define, Mean: Arm1 125(SD 87), Arm2 124 (SD 65)	1	Saline solution	IV	0.9% saline solution- 3ml/kg/hr x one hour pre and 1ml/kg/hr x 6 hrs post, 7 hrs total, Prior to CM administration After CM administration	
				2	NaHCO3	IV	154 meq/l NaHCO3 in 5% dextrose solution- 3ml/kg/hr x one hour pre and 1ml/kg/hr x 6 hrs post, 7 hrs total, Prior to CM administration After CM administration	
Gulel, 2005 [41]	Ioxaglate	IA	Not specified, Not specified	1	Control	NR		All patients received saline 1ml/kg/h infusion 12 h before-12 h after CM
				2	Nac	Oral	600mg bid, 2days, Prior to CM administration After CM administration	The day before and the day of the day of CM
Gunebakmaz, 2012[42]	Iopromide	IA	61-64, Not specified, Not specified	1	Saline	IV	1ml/kg/h, 18 hrs, staring 12 hrs before the procedure, Prior, during and after CM administration	
				2	Saline + Nebivolol	NR	Hydration as arm 1 + Nebivolol 600mg bid, 4 days, starting 2 days before the procedure, Prior, during and after CM administration	
				3	Saline + NAC	IV	Hydration as arm 1 + NAC 5mg day, 4 days, starting 2 days before the procedure, Prior, during and after CM administration	
Han, 2013[43]	Iopamidol	NR	NR	1	Low-dose Oral Atorvastatin + Oral Probucol	Oral	Atorvastatin 20 mg before bedtime and probucol 250 mg 3 times a day, before procedure.	Intervention information very limited with no mention of any hydration. (for all arms)
				2	High-dose Oral Atorvastatin + Oral Probucol	Oral	Atorvastatin 40 mg at bedtime and probucol 250 mg 3 times a day, with loading dose of atorvastatin 40 mg and probucol 500mg 2 hours before procedure.	
				3	High-dose Oral Atorvastatin	Oral	Atorvastatin 40 mg before bedtime, with loading dose atorvastatin 40 mg 2 hours before procedure.	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Han, 2014[44]	Iodixanol	IA	320 mg iodine/ml	1	IV Normal Saline	IV	IV Isotonic saline (0.9% sodium chloride, 1 mL/kg/h) started 12 hours before and continued for 24 hours after contrast medium administration.	Statin therapy was resumed in both groups 3 days after contrast media administration, following completion of the study endpoints
				2	Oral Rosuvastatin + IV Normal Saline	Oral, IV	Rosuvastatin 10 mg every evening from 2 days before to 3 days after contrast medium administration (total dose of 50 mg rosuvastatin over 5 days)	All participants given IV Isotonic saline (0.9% sodium chloride, 1 mL/kg/h) started 12 hours before and continued for 24 hours after contrast medium administration.
Heguilen, 2013 [45]	Ioversal LOCM	IA	NR	2	IV NaHCO3 in 5% dextrose in water	IV	154 mmol NaHCO3, at 3ml/kg, 2 hours prior to CM administration and 1 ml/kg for 6-12 hours post CM administration.	NaHCO 3 group received 154 mEq/l of sodium bicarbonate in 5 % dextrose in H 2 O, mixed by adding 77 ml of 1,000 mEq/l sodium bicarbonate to 423 ml of 5 % dextrose in H 2 O
				3	NAC + IV NaHCO3 in 5% dextrose in water	Oral, IV	600mg NAC, twice daily., 2 days, Prior to CM administration During CM administration plus 154 mmol NaHCO3, at 3ml/kg, 2 hours prior to CM administration and 1 ml/kg for 6-12 hours post CM administration.	
				4	NAC + IV normal saline in 5% dextrose in water	Oral, IV	600mg NAC plus 154 mmol NaCl solution at 3ml/kg/h, 2 days, Prior to CM administration During CM administration After CM administration	Saline solution given 2 hrs before procedure and 12 hrs after. NAC given in same schedule as Arm3
Holscher, 2008[46]	Iopromide	NR	Not specified	1	Hydration only	IV	500 ml 5% glucose and 500 ml 0.9% NaCl, 12h before and 12 h after	
				2	Hydration plus dialysis	IV	Hydration same as arm 1 + dialysis	Low-flux HD started within 20 min after procedure. Duration: 2 hours
				3	Hydration plus NAC	Oral, IV	Hydration same as arm 1 + NAC	NAC 600 mg x4 (2 doses before and 2 doses after)

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Hsu, 2007[47]	Iohexol, LOCM, Other description, Omnipaque	IA	>1.5ml/kg, Not specified, Define, Mean+/- SD=188.6 +/- 57.9 ml	1	Iv hydration + placebo	Oral, IV	IV 0.45% Saline at rate of 1ml/kg/hr + placebo pills 4 doses total, 2 before procedure and 2 after., 24hrs of IV fluid, 48 hrs of placebo pills, Prior to CM administration After CM administration	Placebo pills looked identical to that containing the NAC but was empty
				2	IV hydration + N-acetylcysteine	Oral, IV	Oral NAC 600mg twice a day. 2 doses before and 2 doses after procedure +IV 0.45% Saline at rate of 1ml/kg/hr 12 hrs before and 12 hrs after procedure, 48h, Prior to CM administration After CM administration	
Hsu, 2012 [48]	IohexolIopromide, Other description, Iobitridol	IV	Iohexol= 350 mgI/L, Iobitridol= 350 mgI/mL, Iopromide= 370 mgI/mL, Not specified	1	Control	IV	0.9% NaCl at 3ml/kg for 60 mins before CECT, then continued at 1 ml/kg/h during and for 6 hrs after procedure. Volume was reduced in patients with congestive pulmonary edema or heart failure, Prior to CM administration During CM administration After CM administration	
				2	Nac	IV	600 mg of NAC in 0.9% NaCl for 60 mins prior to contrast injection, Prior to CM administration	
Izani Wan Mohamed, 2008[49]	Iohexol	IA	Arm 1 mean (SD) = 126.67(94.37)ml Arm 2 mean (SD)=136.73 (100.23)ml	1		IV	Saline (0.45% NS) was given intravenously at a rate of I ml/kg/h 12 hrs before and after coronary angiogram Prior to CM administration After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Izani Wan Mohamed, 2008[49] (continued)				2		Oral, IV	Oral NAC 600mg twice daily for four doses starting 12 hrs before procedure + Saline (0.45% NS) was given intravenously at a rate of I ml/kg/h 12 hrs before and after coronary angiogram Prior to CM administration After CM administration	
Jaffery, 2012 [50]	Iodixanol, IOCM	NR	Not specified,Define, High dose >300ml received by some. others received less than 300ml	1	Hydration	IV	Not specified, 24 hrs, Not stated,	Volumes infused comparable between groups
				2	Nac	IV	6g total-1200mg bolus then 200mg/hr for 24 hrs, 24 hrs, Not stated,	Saline0.9% infusion 1 ml/kg/hr for 24 hr. Patients with clinical evidence of heart failure (volume overload) received only intravenous NAC
Jo, 2008[51]	IOCM	IA	320mg iodine/ml	1	Placebo	Oral	NR, Prior and After CM administration on the same schedule as those receiving active treatment	All patients received intravenous half-isotonic saline at a rate of 1 mg/kg per hour for 12 hours before and 12 hours after coronary catheterization
				2	Simvastatin	Oral	40mg 12 hourly, 2 days. Prior and after cm administration	
Jo, 2009[52]	Iodixanol	IA	Mean volume: Arm2: 203.6 ml Arm2: 216.4 ml	2	Oral NAC + IV 0.45% Saline	Oral, IV	1200mg oral NAC every 12 hours for 2 days. Total 4800mg NAC.	All participants received 0.45% saline at 1 ml/kg/h for 12 hours before and 12 hours after procedure.
				3	Oral Ascorbic acid + IV 0.45% Saline	Oral, IV	3g and 2 g oral ascorbic acid before procedure with 12 hour interval and twice with 2g per 12 hours after procedure.	All participants received 0.45% saline at 1 ml/kg/h for 12 hours before and 12 hours after procedure.

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Jo, 2014[53]	NR	IA	NR	2	Regular Atorvastatin dose	Oral	10mg/day initiated day before PCI and maintained after.	
				3	High Atorvastatin dose	Oral	80mg administered as early as possible before PCI, and maintained at 80mg/day for 5 days post procedure. Dose decreased to 10 mg/day after 5 days and maintained.	
Kama, 2014[54]	Iohexol	NR	All patients given < 100ml contrast	1	IV Normal Saline	IV	1,000ml of 0.9% saline solution at 350ml/hour for 3 hours total, covering before, during and after procedure.	
				2	IV NAC in Normal Saline	IV	150 mg/kg NAC in 1,000ml of 0.9% saline at 350m,l/hour for 3 hours total, covering before, during and after procedure.	
				3	IV NaHCO3 in Normal Saline	IV	150 mEq in 1,000ml of 0.9% saline for 350ml/hour for 3 hours total, covering before, during and after procedure.	
Katoh, 2014[55]	Iopamidol	IA	Mean dose: 370 mg/ml (iodine) Mean contrast volume: Arm1: 159ml, Arm2: 96ml	1	No Right Atrium Hemodiafiltration	IV	IV 0.9% saline, 1ml/kg/hour. Prior, during and after CM admin	IV saline started 12 hours before coronary procedure, continued for 24 hours
				2	Right Atrium Hemodiafiltration	IV, Other: Right Atrium Hemodifiltration (RAHDF)	IV 0.9% saline, 1ml/kg/hour + hemodifiltration with blood suction from right atrium; Saline: 24 hours, RAHDF: 30 min before and contunied until 30min after procedure. Prior, during and after CM admin	IV saline started 12 hours before coronary procedure, continued for 24 hours
Kay, 2003[57]	Iopamidol	IA	at the discretion of MD, Not specified, Not specified	1	Placebo	Oral	Placebo bid, 2 days, Prior to CM administration After CM administration	All pts received saline 0.9% 1ml/kg/h infusion 12h before-6 h after CM
				2	Nac	Oral	NAC 600mg bid, 2 days, Prior to CM administration After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kaya, 2013[56]	Iopromide	IA	Mean Volume Arm1: 147ml Arm2: 158ml	2	Oral Atorvastatin + IV Normal Saline	Oral, IV	80mg of oral atorvastatin before primary PCI.	All patients hydrated with IV normal saline for 12 hours after procedure.
				3	Oral Rosuvastatin + IV Normal Saline	Oral, IV	40 mg of rosuvastatin before primary PCI.	All patients hydrated with IV normal saline for 12 hours after procedure.
Kefer, 2003 [58]	Iohexol, Iopromide	NR	Not specified, Not specified	1	Placebo	IV	Placebo NR, NR, Prior to CM administration After CM administration	Placebo given 12 hrs prior to procedure, and after procedure (time frame and dose not given)
				2	Nac	IV	2400mg, NR, Prior to CM administration After CM administration	1200mg given 12 hrs prior to procedure, and 1200mg after procedure (time frame not given)
Khalili, 2006 [59]	Iohexol	NR	647mg, Not specified, Define, 140ml	1	Saline	IV	1000ml normal saline, NS, Prior to CM administration	Saline given at 1ml/kg/h
				2	NAC + saline	IV	1000ml normal saline + 1200mg NAC daily, 2 days, Prior to CM administration During CM administration	NAC given day prior to imaging and day of CM infusion
Kim, 2010[60]	Iodixanol, Iopamidol, Other description, Iobitridol	IA	Define, 39+/-24min for treatment group and 46+/-30 for control group, Define, 201+/-144ml for treatment group and 216+/-166 for control group	1	Control	NR	Not stated	Physiological (0.9%) saline was given intravenously at a rate of 1 ml/kg of body weight per hour for 12 h before and 6 h after coronary angiography in both groups.
				2	Nac	Oral	600mg twice a day, 1200mg total, 48hrs, Prior to CM administration During CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kimmel, 2008[61]	Iomeprol	IA	Not specified	1	Placebo	Oral	NR, 48 hrs, Prior to CM administration During CM administration	Day before and day of procedure All patients received a peri-procedural intravenous infusion (‘volume expansion’) of 1 ml/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to CM)
				2	Nac	Oral	600mg b.i.d, 48 hrs, Prior to CM administration During CM administration	Day before and day of procedure
				3	Zinc	Oral	60mg daily, 24 hrs, Prior to CM administration	Day before
Kinbara, 2010[62]	Iopamidol,	IA	0.755g/ml	1	Hydration	IV	1ml/kg/hr, 30min before and 10hrs after angiography, prior and after CM administration	All arms given normal saline
				2	Hydration and aminophylline	IV	250mg +control treatment, 30min before+control treatment, Prior to CM administration	
				3	Hydration and N-acetylcysteine	Oral	704mg twice daily+control treatment, day before and during procedure+control, prior and during CM administration	
Koc, 2012[63]	Iohexol	IA	Mean Volume: Arm1 130ml, Arm2 130ml Arm3 120ml	1	Standard NS	IV	0.9% saline 1 mL/kg/, 12 hours before and 12 hours after the coronary procedure	
				2	IV NAC + High dose NS	IV	IV bolus of 600 mg of NAC twice daily, before and on the day of the coronary procedure	
				3	High dose NS	IV	IV 0.9% saline 1 mL/kg/, before, on and after the day of coronary procedure	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Koc, 2013 [64]	Not specified	IA	Median: Arm1 90ml, Arm2 90ml, Not specified	1	Normal saline	IV	1 ml.kg.hr 0.9% Saline, 24 hrs, Prior to CM administration After CM administration	12 hrs before and 12 hrs after contrast
				2	NaHCO3	IV	154ml of 1000 meq/l NaHCO3, 12 hrs, Prior to CM administration After CM administration	6 hrs before and 6 hrs after contrast
Kooiman, 2014[65]	LOCM, Iodixanol Iomeprol Iobiditrol	IV	Mean dose (iodine): mean 35.5 -36.6 g; Mean volume: mean 104.7 - 105.7 mL	1	Normal saline	IV	2000 mL saline 0.9%, 1000 mL 1 h prior through1000mL 1 h after CM. Prior and After CM.	Duration 2 hours.All patients given normal saline hydration.
				2	IV Sodium Bicarbonate + normal saline	IV	250mL 1.4% bicarbonate, 1 hour prioir to CM.	1h prior CT - NO Bicarbonate hydration post CM. All patients given normal saline hydration.
Kotlyar, 2005[66]	Iopromide, Other description, Ultravist-370, 0.769 mg/ml, 370mg iodine/ml; Schering Berlin, Germany	IA	Not specified, Define, mean 87ml in Arm 1, mean 89 ml in Arm 2 and mean 86ml in Arm 3	1	IV hydration	IV	0.9% saline commenced at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure, NR, Prior to CM administration After CM administration	All patients, scheduled for angiography, received written instruction to drink 1 l of fluid the evening prior to the procedure
				2	NAC 300mg	Oral	IV NAC 300mg +IV Hydration0.9% saline (Nacl at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure), NR, Prior to CM administration After CM administration	NAC was prepared in 100 ml of 5% dextrose and administered over 20 min, 1–2 h before angiography and again 2–4 h after angiography
				3	NAC 600mg	Oral	IV NAC 600mg +IV hydration 0.9% saline (NaCl at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure), NR, Prior to CM administration After CM administration	NAC was prepared in 100 ml of 5% dextrose and administered over 20 min, 1–2 h before angiography and again 2–4 h after angiography

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kumar, 2014[67]	Iohexol Iodixanol	IA	Iohexol: 350 mg Iodixanol: 320 mg	1	IV NS	IV	1ml/kg/hr, 12 hours before and after administration of radio contrast agent	
				2	Oral NAC + IV NS	Oral, IV	600 mg bd, 12 hours before and after administration of radio contrast agent	
				3	Allpurinol + IV NS	Oral, IV	300 mg/day, 12 hours before and after administration of radio contrast agent	
Lawlor, 2007[68]	Not specified	Not specified	Dose: 100-200mg Mean volume: Arm 1:163ml Arm 2:158 Arm 3: 165ml	1	Placebo + IV NS	Oral, IV	IV 0.9 NaCl 1 mL/kg/hr+ placebo(3 mL of 0.9% NaCl in 30 mL of ginger ale), 112 hr of IV hydration before and after	placebo given at same time as NAC was given to Arm 2
				2	IV hydration + oral NAC	Oral, IV	600 mg NAC in 30 mL of ginger ale orally twice daily the day prior to and the day of angiography and 12 hr of IV hydration (0.9 NaCl 1 mL/kg/hr) both prior to and following the procedure, 48hours	Unlimited oral hydration was encouraged in the postprocedure period in all groups
				3	Oral hydration + oral NAC	IV	NAC (600 mg in 30 mL of ginger ale orally twice daily the day prior to and the day of angiography)+outpatient oral hydration preparation of 1,000 mL water in the 12 hr prior to the procedure + followed by IV hydration (0.9 NaCl 1 mL/kg/hr) beginning 1-2 hr prior to the procedure and continuing for a total of 6 hr afterward	Unlimited oral hydration was encouraged in the postprocedure period in all groups

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Lee, 2011 [69]	Iodixanol	IA	Not specified, Define, Mean: Arm1 120ml, Arm2 113ml	1	Saline	IV	0.9% saline, 1 ml/kg/hour, 24 h infusion- 12 h before - 12 h after procedure, Prior to CM administration During CM administration After CM administration	All patients given 1200mg of NAC 2 times a day for 2 days
				2	NaHCO3	IV	154 meq/L 3ml/kg/h before CM-1ml/kg/h after CM, 7 h infusion-1 h before -6 h after, Prior to CM administration During CM administration After CM administration	
Lehnert, 1998 [70]	Iopentol,	IA and IV	3.0ml/kg(SD=0.4) for control and 3.5 ml/kg(SD=0.6) for the hemodialysis group, Not specified	1	Saline	IV	0.9% saline at 83 ml/hour, 24 hours 12 h before contrast, and 12 hours after contrast	If the patient was not on a calcium channel blocker, then 10 mg nitrendipine per 12 hours was scheduled beginning 12 hours before catheterization
				2	Hemodialysis	Other, Vascular accces shaldon catheter (femoral vein)	Hydrations as arm1 High flux hemodialysis at a flow 500 ml/min. for 3 hours started started 63+/- min after last bolus of CM	If the patient was not on a calcium channel blocker, then 10 mg nitrendipine per 12 hours was scheduled beginning 12 hours before catheterization.
Leoncini, 2014 [71]	Iodixanol	IA	Contrast Volume: Mean Arm 1: 138.2 ml, Mean Arm 2: 149.7ml	1	No rosuvastatin	Oral, IV	IV Saline 0.9% 1ml/kg/h 12h before-12h after + NAC 1200mg bid before and after CM	
				2	Rosuvastatin	Oral, IV	Rosuvastatin oral 40 mg at randomization + 20 mg/d for 2 days	Also given IV Saline 0.9% 1ml/kg/h 12h before-12h after + NAC 1200mg bid before and after CM (Arm1 intervention)

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Li, 2012 [72]	Ultravist 370, iodine 370 mg/ml	NR	Not specified	1	Control	Oral, IV	Placebo 80 mg p.o before procedure; IV isotonic saline (0.9%) at a rate of 1 ml/kg/h before the procedure and for 12 h after the procedure, Prior to CM administration After CM administration	after procedure all patients had long term torvastatin treatment 40 mg/day. Iv isotonic saline (0.9%) at a rate of 1 ml/kg/h before the procedure and for 12 h after the procedure, prior to cm administration after cm administration
				2	Atorvastatin	Oral, IV	Atorvastatin load 80 mg p.o before procedure,	
Li, 2014[73]	Iopamidol	IA	Not specified	1	Standard atorvastatin + probucol dose	Oral	Atorvastatin 20mg qn + Probucol 0.25mg tid, treatment A+P started 1-2 days before CM	All participants received IV normal saline 1ml/kg/h 6h before-6h after CM admin
				2	Large atorvastatin + probucol dose	Oral	Atorvastatin 40mg qn + Probucol 0.25mg tid + loading dose 40 mg Atorvastatin/0.5mg Probucol 2 h prior CM, treatment A+P started 1-2 days before CM	All participants received IV normal saline 1ml/kg/h 6h before-6h after CM admin
				3	Large atorvastatin dose	Oral	Atorvastatin 40mg qn + loading dose 40 mg atorvastatin, 2 h prior CM, treatment A started 1-2 days before CM	All participants received IV normal saline 1ml/kg/h 6h before-6h after CM admin
Liu, 2014[74]	Iopamiron or Ultravist	IA	133.36	2	Risovustatin + IV saline	Oral	10 mg 2-3 days pre and 2-3 days post procedure	
			132.37	3	Atorvastatin + IV saline	Oral	20 mg 2-3 days pre and 2-3 days post procedure	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
MacNeill, 2003 [75]	Iopromide, Ioxilan	IA	Not specified, Define, mean 110(sd=57.7)ml overall; 116 +/- 63.3 mL in placebo group and 103 +/- 52.0 in placebo group	1	Placebo	Oral, IV	Oral placebo (same schedule as in Arm 2) + IV 0.45% saline: 1. Pre-treatment: 1 ml/kg/hr x 12 hrs for inpatients and 2 ml/kg/hr x 4 hrs for day-case patients. Postprocedure: all patients were given 0.45% saline at 75 ml/hr x 12 hrs, oral placebo (same schedule as in Arm 2). IV saline: inpatients: total duration of 24 hrs. Day-case patients: 16 hrs total, Prior to CM administration After CM administration	All patients were pretreated with 0.45% saline at a rate of 1 ml/kg/hr for 12 hr for in-patients and 2 ml/kg/hr for 4 hr for day-case patients. See above regarding post-procedural fluids
				2	Nac	Oral, IV	600mg oral NAC at time of randomization, then 4 hrs later (pre-catherization), then 3 additional doses after the procedure at 12-hour intervals + control regimen of IVF, same IV schedule as control; NAC: as above (at least 4 hrs pre-procedure, then for at least 24 hrs post-procedure (after procedure, then 12 hrs later, then 12 hrs later), Prior to CM administration After CM administration	
Manari, 2014[76]	Iodixanol	IA	Not specified	1	IV normal saline	IV	0.9% isotonic normal saline 1ml/kg/hr, 12 hours.	a ll patients received 70-100 IU/kg unfractionated heparin; aspirin at 162 mg or more; 300/600 loading dose of clopidogrel
				2	High-dose infusion of IV normal saline	IV	0.9% isotonic normal saline 3ml/kg/hr for 1 hour followed by normal saline 1 ml/kg/hr for 11 hours	
				3	IV standard bicarbonate	IV	NaCOH3 solution: 154mEq/L sodium bicarb 1 ml/kg/hr, 12 hours	
				4	High-dose IV bicarbonate	IV	NaCOH3 solution: 154mEq/L sodium bicarb 3 ml/kg/hr for 1 hr follwed by 1 ml/kg/hr for 11 hours	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Marenzi, 2003[77]	Iopentol	IA	Not specified	1	Isotonic saline	IV	Saline 0.9% 1ml/kg/h for 24-32 hours (4-8 hours before-18-24 hours after)	Dose was 0.5 ml/kg/hr if ejection fration was less than 40%
				2	Hemofiltration therapy	Continuous venovenous hemofiltration	Hydration as arm 1 + HF started 4-6 h before CM, stopped during procedure and resumed after completion, for 18-24 hours at a flow of 1000 ml/h	Participants received heparin at the start of and during the hemofiltration.
Marenzi, 2006 [78]	Iohexol, LOCM, Other description, 350 mg of iodine per milliliter; Omnipaque, Amersham Health	NR	Define, Arm 1 mean 274;Arm 2mean= 264;Arm 3 mean= 253	1	Placebo	NR		All treated patients and control patients underwent hydration with intravenous isotonic saline (0.9 percent) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram per hour in cases of overt heart failure) for 12 hrs
				2	Standard dose NAC	Oral, IV	Total dose of 3000mg, Prior to CM administration After CM administration	Intravenous bolus of 600 mg of N-acetylcysteine before primary angioplasty and a 600-mg tablet orally twice daily for the 48 hrs after intervention
				3	High dose NAC	IV	Total dose of 6000mg, Prior to CM administration After CM administration	Intravenous bolus of 1200 mg of N-acetylcysteine before intervention and 1200 mg orally twice daily for the 48 hrs after intervention
Marenzi, 2006[79]	LOCM	Not specified	Not specified	1	Isotonic saline	IV	Saline 0.9% 1ml/kg/h for 24 hours (12 hours before-12 hours after)	
				2	Isotonic saline plus hemofiltration after contrast exposure	NR	Hydration as arm 1 + HF for 18-24 hours after CM at a flow of 1000 ml/h	
				3	Isotonic saline plus hemofiltration before and after contrast exposure	NR	Hydration as arm 1 + HF started 4-6 h before CM, stopped during procedure and resumed after completion, for 18-24 hours at a flow of 1000 ml/h	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Masuda, 2007[80]	Not specified	Not specified	Not specified	1	NaCl	IV	3ml/kg/hr before and 1ml/kg/hr during and after the procedure, 1hr, 6hrs, Prior, during and after CM administration	Only reports saline as NaCl
				2	NaHCO3	IV	3ml/kg/hr before and 1ml/kg/hr during and after the procedure, 1hr, 6hrs, Prior, during and after CM administration	Only reports saline as NaCl
Matejka, 2010 [81]	Iodixanol	IA	NS	1	Placebo	IV	IV infusion normal saline before CM - fluids 3days after CM, Prior to CM administration After CM administration	All pts had unrestricted oral fluids before and after the procedure
				2	Theophylline	IV	205.7mg, Theoph-1h infusion before CM in 500 ml normal saline- fluids 3days after CM, Prior to CM administration After CM administration	
Merten, 2004[82]	Iopamidol	NR	796 mOsm/kgH2O, 755mgof iopamidol per milliliter, and 370 mg iodine per milliliter	1	NaCl	IV	3ml/kg per hour for 1 hour before then 1ml/kg per hour during the contrast exposure and for 6 hrs after the procedure, Prior, during and after CM administration	5% dextrose given in all arms
				2	NaHCO3	IV	3ml/kg per hour for 1 hour before then 1ml/kg per hour during the contrast exposure and for 6 hrs after the procedure. Prior, during and after CM administration	5% dextrose given in all arms

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Miner,2004 [83]	Iohexol	IA	Not specified, Define, Arm 1 mean=350ml; Arm 2 mean=344ml	1	Placebo	Oral	NS, one dose every 12 hrs, 24 hrs, Prior to CM administration During CM administration	All patients received intravenous hydration with 0.45% saline at 75 ml/hour for at least 24 hrs beginning at the time of enrollment
				2	Nac	Oral	2000mg/dose x 2-3 doses. Total: 4000-6000mg, one dose every 12 hrs, 24 hrs, prior to cm administration during cm administration	Prior day patients received their first dose at 8 pm the night before their procedure with subsequent doses at 8 am and 8 pm the day of their procedure. Same day patients received their first dose at 8 am the day of their pci procedure with a subsequent dose at 8 pm the same day. Thus, if randomized to nac, prior day patients received a total of 6000 mg of nac while same day patients received a total of 4000 mg.
Motohiro, 2011[84]	Iopamidol, LOCM	IA	Not specified	1	Nacl	IV	1ml/kg/hr of NaCl, 12 hr before and after, Prior, during and after CM administration	Total infusion 24 h - 12h before/12 h after with saline
				2	Bicarbonate	IV	1ml/kg/h (154 meq), 9h - 3 h before-/ 6 h after, Prior, during and after CM administration	
Ochoa, 2004 [85]	Iodixanol, Iohexol, Ioxaglate, Other description, diatrizoate	IA	151 +/-71 mL(placebo group) and 136 +/-78 mL (NAC group), Not specified, Define, Arm 1 mean+/-SD=151 +/-71 mL and Arm 2=136 +/-78 mL	1	Placebo	Oral	5ml 0.9% saline diluted in 20 ml diet cola, 1 hr prior and 4 hr after, Prior to CM administration After CM administration	Saline IV 150 ml/h starting 4hr before and continuing 6 hr after procedure
				2	Nac	Oral	2 doses of NAC (1000 mg (5ml) in 20 ml diet cola, 1 hr prior and 4 hr after, Prior to CM administration After CM administration	Saline IV 150 ml/h starting 4hr before-and continuing 6 hr after procedure

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Oldemeyer, 2003[86]	Iopamidol	IA	Not specified, Define, Mean: Arm1 127ml (sd 73), Arm2 134ml (SD 71)	1	Placebo	Oral	Placebo in 120 ml bev every 12 h/ 4 doses, 2 days, Prior to CM administration After CM administration	Starting the night before CM All pats received saline 0.45% 1ml/kl/h infusion 12h before-12h after CM
				2	Nac	Oral	NAC 1500 mg diluted in 120ml bev - every 12 h/4 doses, 2 days, Prior to CM administration After CM administration	Starting the night before CM
				3	Saline + NAC	Oral, IV	1ml/kg/h + NAC 600 mg bid starting the day before CM, 12 h inf (6 h before -6 h after), Prior to CM administration During CM administration After CM administration	
Ozcan, 2007[87]	Ioxaglate LOCM	IA	Median: 110 ml (25-300), Not specified, Define, comparable between groups	1	IV normal saline	IV	1ml/kg/h, 12 h inf (6 h before -6 h after), Prior to CM administration During CM administration After CM administration	154 meq
				2	Oral NAC + IV normal saline	Oral, IV	600mg oraly wice daily day before and day of procedure plus saline protocol in Arm 1	154meq
				3	IV NaHCO3 in 5% dextrose in water	IV	154 mL of 1000-mEq/L sodium bicarbonate to 846 mL of 5% dextrose in water plus saline protocol in Arm 1	
Ozhan, 2010[88]	Iopamidol	IA	Not specified, Define, comparable between groups	1	Nac	Oral	NAC 600 mg twice daily, day after procedure, 1 day, After CM administration	Saline 1000 ml infusion for 6 h after procedure
				2	Nac + atorvastatin	Oral	NAC 600 mg and Atorvastatin 80 mg twice daily on day 1 after procedure. Atorvastatin 80mg d for 2 days after procedure, 3 days, After CM administration	Saline 1000 ml infusion for 6 h after procedure

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Patti, 2011 [89]	Iobitridol	IA	915 mOsm/kg, Not specified, Define, Mean: Arm1 213ml (SD 13), Arm2 209ml (SD72)	1	Placebo	Oral	Placebo, not specified, first dose 12 hrs before and another dose 2 hrs before procedure, Prior to CM administration	All patients received 40mg/day of atorvastatin after PCI.
				2	Atorvastatin	Oral	Total 120mg (80mg and 40mg doses), 80mg 12 hrs before procedure and 40mg 2 hrs before procedure, Prior to CM administration	
Poletti, 2007[90]	Iopromide	IV	2 mL/kg body weight was used for nonneurologic indications, and a standard dose of 100 mL was used for brain imaging or suspicion of pulmonary embolism,	1	Hydration plus placebo	IV	N/A, 1hr before and up to 12hrs after, Prior to CM administration After CM administration	Each patient was assigned to receive 0.45% saline solution IV at a rate of 5 ml/kg body weight over the course of the hour before CT and followed at a rate of 1 ml/kg body weight for 12 hrs after CT. Each patient was assigned to receive 0.45% saline solution IV at a rate of 5 ml/kg body weight over the course of the hour before CT and followed at a rate of 1 ml/kg body weight for 12 hrs after CT.
				2	Hydration plu N-acetylcysteine	IV	900mg before and 900mg after, 1hr before and up to 12hrs after, Prior to CM administration After CM administration	Each patient was assigned to receive 0.45% saline solution IV at a rate of 5 ml/kg body weight over the course of the hour before CT and followed at a rate of 1 ml/kg body weight for 12 hrs after CT.
Qiao, 2015[91]	Iodixanol	IA	212 ml	1	IV saline	IV	(0.9% sodium chloride 1-1.5 ml/kg/hour for 3-12 hours before and 6-24 hours after the procedure).	
			204 ml	2	Rosuvastatin+IV saline	Oral	10 mg everyday for at least 48 hours before and 72 hours after CM administration.	(0.9% sodium chloride 1-1.5 ml/kg/hour for 3-12 hours before and 6-24 hours after the procedure).

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Quintavalle,2012 [92]	Iodixanol	IA	Not specified	1	Control	NR	Only CKD prophylaxisis	All patients received CKD prophylaxisis : NAC 1200 mg orally twice daily the day before and day of administration of contast and NaHCO3 (154 meq/L in dextrose and H2O), 3 ml/kg/hr 1 hour before and 1 ml/kg/hr for 6 hrs after contrast
				2	Atorvastatin	Not reported,	80mg, within 24 hrs of procedure, Prior to CM administration	
Rashid, 2004[94]	Iohexol	IA	135.4 +/- 62.7 ml NAC group, 151.2 +/- 75.6 ml placebo group	1	IV Normal Saline	IV	500 ml saline infusion, twice	Both groups got 500 ml over 4-6 hrs before procedure and another 500 ml over 4-6 hrs after procedure
				2	IV Normal Saline + Oral NAC	Oral, IV	NAC 1 g per 500 ml saline infusion before and after CM	Both groups got 500 ml over 4-6 hrs before procedure and another 500 ml over 4-6 hrs after procedure

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Ratcliffe, 2009 [93]	Iodixanol, IOCM	IA	Was not standardized due to variation among patients	1	IV normal saline in 5%dextrose in water	IV	Normal saline (0.9% saline in 5% dextrose) at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure.	
				2	IV and oral NAC + IV normal saline in 5% dextrose in water	Oral, IV	IV bolus of 1200 mg of NAC 1 h before intervention and 1200 mg orally twice daily for 48 h after intervention + IV NaCl (154 meq/L NaCl in 5% dextrose), at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure, with normal saline as Arm 1	
				3	IV NaHCO3 in 5% dextrose in water	IV	IV NaHCO3 (154 ml of 1000 meq/L NaHCO3 to 846 ml of 5% dextrose, slightly diluting the dextrose concentration to 4.23%) at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure..	
				4	NaHCO3 plus NAC	Oral, IV	IV bolus of 1200 mg of NAC 1 h before intervention and 1200 mg orally twice daily for 48 h after intervention + NaHCO3 (154 ml of 1000 meq/L NaHCO3 to 846 ml of 5% dextrose, slightly diluting the dextrose concentration to 4.23%) at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure.	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Reinecke, 2007 [95]	Iopromide, IOCM, Other description, (Ultravist 370TM, Schering AG, Berlin, Germany).	NR	Arm1:mean 188; Arm 2 mean184; Arm3 mean197mg/dl, Not specified	1	Hydration only	IV	Glucose 5% + Saline 0.9% 24 h (2000 ml 12 h before- 12 h after CM	
				2	Hydration + dialysis	IV, Other, hemodialysis	Hydration as arm 1 + Low-flux HD started within 20 min after procedure. Duration: 2 hours	
				3	Hydration + NAC	Oral, IV	Hydration as arm 1 + NAC 600 mg x4 (2 doses before and after)	One dose NAC 600 mg was given at the evening before catheterization, the second dose was given on the morning before catheterization; the third was given at the evening after catheterization and the last dose was given on the morning the day after angiography.

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Sadat, 2011[96]	Iopamidol	IA	Not specified	1	IV Hydration only	IV	1 L iv infusion over a period of 12 hrs before angiography and 1 L over 12 hrs following the procedure)., 24 hrs, Prior to CM administration After CM administration	12h before and 12h after
				2	Hydration+NAC	Oral	Oral NAC 600 mg twice daily the day before the angiogram and 600 mg twice on the day of the angiogram along with iv fluids, 48 hrs, Prior to CM administration During CM administration After CM administration	Day before and day of procedure
Sandhu, 2006 [97]	Iodixanol, Iopamidol	IA	Not specified, Define, 150.9 ml +/- 78.6 in NAC group, 125.4 +/- 67.4 ml in control group	1	Control	Not reported		They do not specify if NAC is oral , Hydration not part of protocol, left up to physician
				2	Nac	Not reported	NAC 600mg bid, the day before and the day of the procedure, Prior to CM administration	They do not specify if NAC is oral , Hydration not part of protocol, left up to physician
Sanei, 2014[98]	Iopromide	IA	100	1	Placbo	Oral	Placebo (2 tablets) from 24 hr before to 48 hr after CM administration	No information on other administrations
				2	Atorvastatin	Oral	80mg (2 40 mg tablets): from 24 hr before to 48 hr after CM administration	
Sar, 2010[99]	Iohexol	IV	Dose: 300mg/100ml	1	IV Normal Saline	Oral, IV	NaCl 0.9% 1ml/kg 12h prior-24 h after	
				2	Oral NAC + IV Normal Saline	Oral, IV	NAC 1200 mg/d, 1h prior CT and 2 d after for a total of 3 days, and NaCl 0.9% 1ml/kg 12h prior-24 h after	
Seyon, 2007[100]	Iohexol	IA	147.5+/- 74.5 ml (tc); 133.68+/-58.04 (control)	1	Placebo+hydration	Oral	Placebo similar to NAC, once before procedure and then twice daily after for total of 4 doses. Prior and After CM administration	IV saline 0.45% 1 ml/kg/hr; 4-6 hrs pre and 12 hrs post

				2	N-Acetylcysteine+hydration	Oral	600mg, once before procedure and then twicw daily after for total of 4 doses. Prior and after cm administration	Iv saline 0.45% 1 ml/kg/hr; 4-6 hrs pre and 12 hrs post

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Shavit, 2009 [101]	Iopamidol LOCM	NR	755 mg iopamidol per milliliter, and 370 mg iodine per milliliter, Not specified	1	IV NaHCO3 in 5% dextrose in water	IV	154 mq/L NaHCO3 in 5% dextrose. The initial IV bolus was 3 ml/kg for 1 hour before cardiac catheterization. Following this bolus, patients received the same fluid at a rate of 1 ml/kg per hour during the contrast exposure and for 6 hrs after the procedure, .	
				2	Oral NAC + intravenous normal saline	Oral, IV	NAC 600 mg× 2/d PO the day before and the day of the procedure., 2d, Prior to CM administration plus sodium chloride at 1 ml/kg/hr for 12 hours prior to infusion	
Shehata, 2015[102]	Iopromide	IA	In boluses of 15-20ml	1	Placbo	Oral	Placebo formal matching Ator.	IV saline + N-acetylcysteine (1200 mg)
				2	Atorvastatin + IV saline	Oral	(80 mg daily) for 48 h before PCI	IV saline + N-acetylcysteine (1200 mg)
Shyu, 2002 [104]	Iopamidol LOCM	NR	0.755mg/ml, Not specified	1	NAC + 0.45% saline	Oral, IV	Placebo, placebo, Prior to CM administration After CM administration	Placebo + 0.45% saline, saline given 12 hrs before and 12 hrs after procedure
				2	0	Oral, IV	400mg, twice a day, 2 days, Prior to CM administration During CM administration After CM administration	NAC given orally day before procedure and day of procedure. 0.45% saline given by IV. Saline given 12 hrs before and 12 hrs after procedure
Spargias, 2004[103]	IOCM, LOCM	IA	Mean volume: Arm1: 261 ml Arm2: 287 ml	1	Placebo + IV Normal Saline	Oral, IV	Oral placebo, given as 2 tablets2 hours before angiography and 2 g the night and morning after	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.
				2	Oral Ascorbic Acid + IV Normal Saline	Oral, IV	3g oral ascorbic acid, given 2 hours before angiography and 2 g the night and morning after	All participants received IV Normal Saline rate of 50-125 ml/h from randomization until 6 hours after procedure.

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Tanaka, 2011[105]	Iopamidol, LOCM	IA	755mg/ml, range 205-216 +/- 80	1	Placebo	Oral	4 ml of water	Ringer lactate 1-2 ml/kg/h for 12 hr after pci Volume of cm given per arm, comparable, dose not specified
				2	Nac	Oral	705 mg every 12 h/ total 2820, 36 hrs	Ringer lactate 1-2 ml/kg/h for 12 hr after pci
Tepel, 2000 [106]	Iopromide	IV	75 mL of .623g /mL with 300mg/mL iodine, Not specified, Define, • 75 mL of .623g /mL with 300mg/mL iodine	1	Not in PC Tables	IV	Placebo-N/A, Saline 1ml/kg 12 hrs before and 12 hrs after administration, 24 hrs, Prior to CM administration During CM administration After CM administration	
				2	Not n PC Tables	Oral, IV	Acetylcysteine 600mg orally twice daily before and on day of contrast administration, Saline 1ml/kg 12 hrs before and 12 hrs after administration, 2days, Prior to CM administration During CM administration After CM administration	Plus placebo
				3	Not in PC Tables			
				4	Not in PC Tables			

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Thayssen, 2014[107]	Iodixanol (given to "almost all patients", no further details)	IA	Duration: mean 19 minutes Volume: mean 130-150 ml	1	IV Normal Saline	IV	IV 0.9% isotonic saline given ≥60ml/h for minimum 6 hours.	
				2	IV Normal Saline + oral NAC	Oral, IV	NAC 1200 mg/d (1200 mg before and 1200mg/d for 48h). Prior and after CM administration	All patients received IV 0.9% isotonic saline given ≥60ml/h for minimum 6 hours (from Arm1)
				3	IV Normal Saline + IV NaHCO3	IV	NaHCO3 500ml/1h then 100ml/h for 5 hours Prior, during, and after CM administration	All patients received IV 0.9% isotonic saline given ≥60ml/h for minimum 6 hours (from Arm1)
				4	IV Normal Saline + oral NAC + IV NaHCO3	Oral, IV	NAC 1200 mg/d (1200 mg before and 1200mg/d for 48h), plus NaHCO3 500ml/1h then 100ml/h for 5 hours. Prior, during, and after CM administration	All patients received IV 0.9% isotonic saline given ≥60ml/h for minimum 6 hours (from Arm1)

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Thiele, 2010[108]	Iopromide	IA	Not specified, Define, median=180 ml	1	Placebo	IV	10ml of NaCl 0.9% before angio, 10 mls twice daily for 48h after PCI, 48 hrs, Prior to CM administration After CM administration	After PCI, all treated and control patients underwent hydration with intravenous NaCl (0.9%) infusion at a rate of 1ml/kg of body weight per h for 12 h (or 0.5ml/kg/h in overt heart failure)
				2	Nac	IV	1,200mg twice daily, 6000mg, 48 hrs, Prior to CM administration After CM administration	IV bolus of 1,200 mg before angioplasty and 1,200 mg intravenously twice daily for the 48 h after PCI (total dose 6,000 mg
Toso, 2010[109]	Iodixanol	IA	Not specified	1	Placebo	Oral	Placebo NR, 4 days - starting 48 h before CM-48 h after, Prior to CM administration After CM administration	Saline 1ml/kg/h infusion 12h before CM-12 after + NAC VO 1200mg bid 1 day before CM and day after
				2	Atorvastatin	Oral	Atorvastatin 80mg/d, 4 days - starting 48 h before CM-48 h after, Prior to CM administration After CM administration	Saline 1ml/kg/h infusion 12h before CM-12 after + NAC VO 1200mg bid 1 day before CM and day after
Traub, 2013[110]	Iodixanol, Iopamidol, Ioversol	IV	Not specified	1	IV Normal Saline	IV	500ml normal saline 30min infusion pre CM then infusion 67ml/h), a min 2.5 hours, prior, during and after CM admin	Postcontrast infusion was stopped when one of the following occurred: the patient was discharged, the post-CT infusion was stopped at the discretion of the clinical team caring for the patient, the patient was discharged from the hospital, or 24 hours elapsed, symptomatic hypotension requiring treatment, altered mental status, respiratory distress, pulmonary edema, oropharyngeal edema or bronchospasm requiring treatment, severe urticaria or patient discomfort

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Traub, 2013[110] (continued)				2	IV NAC + IV Normal Saline	IV	NAC 3g in 500ml normal saline 30min infusion pre CM then infusion 200mg/h (3g in 1000ml at 67ml/h), a min 2.5 hours, prior, during and after CM admin	
Ueda, 2011[111]	Iohexol, Iopamidol,	IA	Not specified	1	NaCl	IV	0.5 ml/Kg bolus, Prior, during and after CM administration	Followed by infusion at 1ml/kg/h for 6 hr Volumes were comparable. Given at the discretion of MD
				2	NaHCO3	IV	154 meq/L bolus, Prior, during and after CM administration	
Vasheghani-Farahani, 2010 [112]	Iohexol	IA	Not specified, Define, 123 arm 1- 112 arm 2	1	Saline	IV	Saline 0.45% - 1075ml, 7h infusion (1 h prior- 6h after), Prior to CM administration During CM administration After CM administration	Infusion- 3ml/kg/h prior CM then 1ml/kg/h
				2	Bicarbonate	IV	Saline 0.45% 1000ml + 75ml 8.4% bicarbonate, 7h infusion (1 h prior- 6h after), Prior to CM administration During CM administration After CM administration	Infusion- 3ml/kg/h prior CM then 1ml/kg/h
Vogt, 2001[113]	LOCM	Not specified	Not specified	1	IV saline	IV	1 ml/kg/hr, 24 hrs (12 hrs before and after contrast administration)	
				2	IV saline/Hemodialysis	IV, hemodialysis	Hydration as arm 1 + High-flux HD started between 30 and 280 min after first bolus of CM Duration: 3 hours	Hd: high-flux polysulphone membrane (f50 or f60)). The mean blood flow was 180

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Wang, 2008[114]	Iopromide	IA	Mean Volume: 103.48ml control group, 82.13ml NAC group	1	IV Normal Saline	IV	Normal saline hydration, during procedure and 10 hours after	
				2	IV NAC + IV Normal Saline	Oral	5g NAC + normal saline hydration, during procedure and 10 hours after	
Webb, 2004 [115]	Other description, Ioversol	IA	Not specified, Define, Median 120 ml in both groups	1	Placebo	IV	50ml of 5% dextrose saline, 15 minutes, Prior to CM administration	Placebo Study solution was administered within 15 minutes 1 hrs prior to contrast procedure. According to abstract but not in text, all patients received 200 ml NS prior to procedure and 1.5 ml/kg/h for 6 hr after procedure
				2	Nac	IV	50ml of 5% dextrose saline + 500mg NAC, 15 minutes, Prior to CM administration	NAC mixed into saline and given intravenously
XinWei, 2009[116]	Iodixanol (in patients with CKD) Iohexol (all other patients)	IA	Body weight (kg) x 5ml/SrCr.	1	Simvastatin 20	Oral	20mg/day from admission to the day before PCI, and then resumed simvastatin 20 mg/day for the following days, Up to 48hrs after procedure. Prior and After CM administration	All patients were hydrated with intravenous isotonic saline (0.9%) at a rate of 1 ml/kg body weight per hour for 6 to 12 hrs before and 12 hrs after coronary catheterization to achieve a urinary flow rate of ≥150 ml/hour within 6 hours after PCI.
				2	Simvastatin 80	Oral	80mg/day from admission to the day before PCI, and then resumed simvastatin 20 mg/day for the following days. Up to 48hrs after procedure. Prior and After CM administration	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Yeganehkhah, 2014[117]	Iohexol	IA	Average dose: Arm 1: 41.9ml Arm 2: 45.7 ml Arm 3: 45.1ml	1	IV NS	IV	3 mL/kg/ 1218 Yeganehkhah MR, Iranirad L, Dorri F, et al hour of Na bicarbonate, an hour prior to angiography and 1 mL/kg/hour, within six hours after angiography.	
				2	NaHCO3 + IV NS	IV	oral NAC (600 mg twice a day) one day before angiography and on the day of angiography, in addition to isotonic normal saline (1 mL/kg/hour; maximum 100 mL/hour) for 12 hours before and after angiography.	
				3	Oral NAC + IV NS	Oral, IV	isotonic normal saline (1 mL/kg/hour; maximum 100 mL/hour) was prescribed for 12 hours, before and after angiography.	

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Yun, 2014[118]	Iodixanol Iohexol (not analyses seperately)	IA	Arm 1: 226 ml Arm 2: 216ml	1	IV normal saline	IV	(0.9% sodium chloride, 1 mL/kg/h) was performed during the pre- and post-PCI periods at the physician's discretion. Hydration rate was reduced to 0.5 mL/kg/h for patients with a left ventricular ejection fraction (EF) <40%.	All patients received: Aspirin (300 mg/day) and clopidogrel (300 mg/day) were loaded in all patients before the procedure. An intravenous bolus of 5000 U unfractionated heparin was given, and additional heparin boluses were given to maintain activated clotting time >300 seconds during the procedure. Coronary angiography and stent implantation were performed using standard interventional techniques. Platelet glycoprotein IIb/IIIa inhibitors were administered according to operator preference. Aspirin (100 mg/day), clopidogrel (75 mg/day), and statins were prescribed to all patients after the procedure.
				2	Risovustatin + IV normal saline	Oral	40 mg Plus hydration: (0.9% sodium chloride, 1 mL/kg/h) was performed during the pre- and post-PCI periods at the physician's discretion. Hydration rate was reduced to 0.5 mL/kg/h for patients with a left ventricular ejection fraction (EF) <40%.	
Zhang, 2015[119]	Iodixanol (moderate contrast volume)	IA	200–300ml	1	Placebo	Oral	Blank control 2 days before to 3 days after contrast medium administration.	Hydration administered at the physician's discretion
				2	Rosuvastatin	Oral	10 mg 2 days before to 3 days after contrast medium administration.	Hydration administered at the physician's discretion
Zhang, 2015[119]	Iodixanol (high contrast volume)	IA	>300ml	1	Placebo	Oral	Blank control 2 days before to 3 days after contrast medium administration.	Hydration administered at the physician's discretion
				2	Rosuvastatin	Oral	10 mg 2 days before to 3 days after contrast medium administration.	Hydration administered at the physician's discretion

Evidence Table E-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Zhou, 2012[120]	Iodixanol, Iopromide, Iohexol	IA	Mean volume: Arm1: 133.7 ml Arm2: 136.4 ml	1	IV Normal Saline	IV	IV Normal Saline at 1mg/kg/h for 4 hours before and at least 12 hours after procedure.	
				2	IV and Oral Ascorbic Acid + IV Normal Saline	Oral, IV	3g ascorbic acid IV injection before procedure, then oral 0.5 g ascorbic acid every 12 hours for 2 days after procedure. Total 5 g administered IV and Oral	All participants given IV Normal Saline at 1mg/kg/h for 4 hours before and at least 12 hours after procedure.

ACEI= Angiotensin Converting Enzyme Inhibitor, ANP=Atrial Natriuretic Peptide, AVH= Amlodipine Valsartan Hydration, b.i.d=Bi-daily, Bev=Beverage, CAG=Coronary Angiogram, Cc/hr= cubic centimeter per kilogram, CECT=Contrast Enhanced Computed Tomography, CM=Contrast Media, H=Hour, HD=Hemodialysis, hrs=hrs, IA=Intrarterial, IOCM=Iso-Osmolar Contrast Media, IQR=Interquartile Range, IV=Intravenous, IVF=Intrvenous Fluid, LCA=Left Coronary Artery, LOCM=Low-Osmolar Contrast Media, Mcg/kg/min=microgram per kilogram per min, MD= Doctor of Medicine, mEq/l= milliequivalents per liter, Mg/dl=milligram per deciliter, Mg/kg/hour=milligram per kilogram per hour, Mg/kg=milligram per kilogram, Mg=milligram, mls=milliliters, mOsm/kg= milliosmoles per kilogram, N/A=Not Applicable, NAC=N-acetylcysteine, NaCl=Sodium Chloride, NaHCO3=Sodium Bicarbonate, NR=Not Reported, NS=Normal Saline, Osm=Omsolarity, p.o.=By Mouth, PCI=Percutaneous Coronary Intervention, PCWP=Pulmonary Capillary Wedge Pressure, POBID=By mouth twice daily, RCA=Right Coronary Artery, SB=Sodium Bicarbonate, SD=Standard Deviation, Ug/kg/min=microgram per kilogram per minute, VO=Vocal Order

Evidence Table E-4. Summary of studies comparing N-acetylcysteine versus IV saline with or without placebo for the prevention of contrast induced nephropathy and other outcomes

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	NAC route	Definition of CIN*	Study limitations†
ACT, 2011[3]	Placebo+ NS vs. NAC+ NS	2308	Cr <176umo/L, with PCI	68	892 (39)	30 days	LOCM, IOCM, HOCM IA	Oral	A1	L
Alioglu, 2013[6]	0.45% saline vs. NAC + 0.45% saline	113	General	63-61	38 (34)	48 hours	LOCM (Iomeprol) IA	Oral	A1	H
Allaqaband, 2002[7]	0.45% saline vs. NAC + 0.45% saline	123	Cr >1.6mg/dl, or CrCl <60ml/min	70-71	52 (42)	48 hours	LOCM, IOCM IA	Oral	A2	M
Amini, 2009[8]	Placebo+ NS vs. NAC+ NS	90	CKD	63-65	36 (40)	48 hours	LOCM, IOCM IA	Oral	A3	M
Aslanger, 2012[9]	Placebo + NS vs. high-dose NAC + NS	312	STEMI	56	71 (23)	72 hours	LOCM (Ioxaglate) IA	IV	A1	M
Awal, 2011[10]	NS vs. NAC+ NS	100	Coronary Heart disease	52-58	18 (18)	24 hours	NR IA	Oral	A3	H
Azmus, 2005[11]	Placebo + NS vs. NAC + NS	397	Cr >1.3mg/dl, diabetes, or >70 years	66	163 (41)	48 hours	LOCM (Ioversol, Iohexol, Iopamidol), HOCM (diatrizoate) IA	Oral	A3	L
Baker, 2003[12]	NS vs. NAC+ NS	80	Cr >1.36mg/dl or CrCl <50ml/min	67	10 (13)	96 hours	IOCM (Iodixanol) IA	Oral	A1	M
Baranska-Kosakowska, 2007[14]	NS vs IV NAC + NS	112	Heart transplant patients	55-57	11 (10)	NR	LOCM IA	IV	NR	
Baskurt, 2009[13]	NS vs. NAC+ NS	217	Moderate CKD	67	87 (40)	12 months	LOCM (Ioversol) IA	Oral	A2	H
Boccalandro, 2003[17]	Placebo + 0.45% saline vs. NAC + 0.45% saline	179	Cr >1.2 mg/dl or CrCl <50ml/min	66	71 (40)	48 hours	IOCM (Iodixanol) IA	Oral	A2	H
Briguori, 2002[21]	0.45% saline vs. NAC + 0.45% saline	183	Cr >1.2mg/dl, CrCL <70ml/min	55-73	25 (14)	5 days	LOCM (Iopromide) IA	Oral	A1	M
Brueck, 2013[23]	Placebo+ NS vs. IV-NAC+ NS vs. IA-NAC+ NS	499	Cr concentration of ≥1.3 mg/dL	69-79	144 (29)	72 hours	LOCM (Iopromide) IA	IV	A2	L
Burns, 2010[24]	Placebo + NS vs. NAC + NS	42	General	NR	NR	5 days	NR, NR	IV	A2	M
Buyukhatipoglu, 2010[25]	NS vs. IV NAC + NS	60	Coronarty artery disease	59-62	18 (30)	24 hours	LOCM (Iobitridol) IA	IV	NR	
Carbonell, 2007[26]	Placebo + 0.45% saline vs. NAC + 0.45% saline	216	General	50-78	51 (24)	48 hours	LOCM (Iopromide) IA	IV	A3	L

Evidence Table E-4. Summary of studies comparing N-acetylcysteine versus placebo or usual care for the prevention of contrast induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	NAC route	Definition of CIN*	Study limitations†
Carbonell, 2010[27]	Placebo + 0.45% saline vs. NAC + 0.45% saline	81	Cr >1.4 mg/dL	69-70	16 (20)	2 days	LOCM (Iopromide) IA	IV	A3	L
Castini, 2010[28]	NS vs. NAC+ NS	156	Cr >1.2 mg/dl	63-81	19 (12)	5 days	IOCM (Iodixanol) IA	Oral	A1	M
Chousterman, 2013[30]	NS vs. NAC + NS	140	ICU patients	47-73	NR	72 hours	LOCM (Iohexol) IA	Oral	A3	H
Demir, 2008[31]	NS vs. NAC+ NS	97	General	56-62	43 (44)	3 days	LOCM (Iomeprol, Iopamidol) IV	Oral	A3	H
Durham, 2002[32]	0.45% Saline vs. high-dose NAC + 0.45% saline	79	Baseline Cr >1.7 mg/dL	69-71	27 (34)	144 hours	LOCM (Iohexol) IA	Oral	A2	M
Erturk, 2014[34]	IV Normal Saline vs. Oral NAC + IV Normal Saline vs. IV NAC + IV Normal Saline	307	Moderate to severe renal dysfunction	65-67	112 (36.5)	1 year	LOCM (Iopromide) IA	Oral, IV	A3	M
Ferrario, 2009[35]	Placebo+ NS vs. NAC+ NS	200	Moderate to severe chronic renal failure	75	70 (35)	3 days	IOCM (Iodixanol) IA	Oral	A3	M
Fung, 2004[37]	NS vs. NAC + NS	91	Moderate to severe renal impairment	68	27 (30)	48 hours	LOCM (Iopromide) IA	Oral	A3	M
Goldenberg, 2004[38]	Placebo + 0.45% saline vs. NAC + 0.45% saline	80	Chronic renal insufficiency	69-71	14 (18)	7 days	LOCM (Iopamidol) IA	Oral	A1	L
Gomes, 2005[39]	Placebo + NS vs. NAC + NS	156	High risk for CIN	64-67	64 (41)	48 hours	LOCM (Ioxaglate) IA	Oral	A2	L
Gulel, 2005[41]	NS vs. NAC + NS	50	Cr >1.3	49-73	13 (26)	48 hours	LOCM (Ioxaglate) IA	Oral	A2	M
Gunebakmaz, 2012[42]	Saline + NS vs. NAC + NS	120	Cr >1.2 mg/dl	64 -66	37 (31)	5 days	LOCM (Iopromide) IA	NR	A3	H
Holscher, 2008[46]	NS + glucose vs. NAC +NS + glucose	412	General	67-71	136 (33)	30 days	LOCM (Iopromide) IA	Oral	A2	H
Hsu, 2007[47]	NS vs. NAC+ NS	20	Cr ≥1.6mg/dl or eGFR <40ml/mi, diabetic patients	44-84	10 (50)	5 days	LOCM (Iohexol) IA	Oral	A3	M

Evidence Table E-4. Summary of studies comparing N-acetylcysteine versus placebo or usual care for the prevention of contrast induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	NAC route	Definition of CIN*	Study limitations†
Hsu, 2012[48]	NS vs. NAC+ NS	240	General	80	53 (22)	72 hours	LOCM (Iohexol, Iobitridol, Iopromide) IV	IV	A2	H
Izani Wan Mohamed, 2008[49]	0.45% saline vs. NAC + 0.45% saline	100	Renal impairment	56-58	16 (16)	48 hours	LOCM (Iohexol) IA	Oral	A3	L
Jaffery, 2012[50]	Hydration + NS vs. high-dose NAC + NS	398	Myocardial infarction (MI)†	66	146 (37)	72 hours	IOCM (Iodixanol) IV	IV	A1	H
Kama, 2014[54]	IV Normal Saline vs IV NAC in Normal Saline vs IV NaHCO3 in Normal Saline	107	High risk of CIN, using Mehran score (>5 points)	71	48 (45)	1 month	LOCM (Iohexol) Route NR	IV	A3	M
Kay, 2003[57]	Placebo + NS vs. NAC + NS	200	Cr >1.2mg/dl- CrCl <60ml/min	69	77 (39)	7 days	LOCM (Iopamidol) IA	Oral	A1	M
Kefer, 2003[58]	Placebo + dextrose vs. high-dose NAC + dextrose	104	General	61	24 (23)	24 hours	LOCM (Iohexol, Iopromide) IA	IV	A3	L
Khalili, 2006[59]	NS vs. NAC+ NS	70	Cr >1.2mg/dl- CrCl <60ml/min	74	28 (40)	72 hours	LOCM (Iohexol) IA	Oral	A1	H
Kim, 2010[60]	NS vs. NAC + NS	166	Cr >1.5mg/dl	62	66 (40)	48 hours	IOCM (Iodixanol), LOCM (Iopamidol) IA	Oral	A3	M
Kimmel, 2008[61]	Placebo + 0.45% saline vs. NAC + 0.45% saline	54	Cr >1.2mg/dl- CrCl <50ml/min	66-71	14 (26)	2 days	LOCM (Iomeprol) IA	Oral	A2	M
Kinbara, 2010[62]	NS vs. high-dose NAC + NS	45	Stable coronary artery disease	70-71	17 (38)	48 hours	LOCM (Iopamidol) IA	Oral	A2	M
Koc, 2012[63]	Standard NS vs. IV NAC + High dose NS vs. High dose NS	220	CrCL≤60 ml/min or SrCr ≥1.1 mg/dl	62-65	50 (23)	48 hours	LOCM (Iohexol) IA	IV	A3	
Kotlyar, 2005[66]	NS vs. NAC + NS	60	Cr concentrations ≥0.13 mmol/l	66-69	10 (33)	30 days	LOCM (Iopromide) IA	IV	A2	M
Kumar, 2014[67]	IV Normal Saline vs. Oral NAC + IV Saline	180	Coronary block	65	110 (22)	5 days	LOCM (Iohexol) IOCM (Iodixanol) IA	Oral	NR	H
Lawlor, 2007[68]	Placebo + IV NS vs. IV hydration + oral NAC vs. Oral hydration + oral NAC	78	SrCr < 140 umol/l or CrCl <50 ml/min	NR	NR	48 hours	NR IA	Oral	A3	
MacNeill, 2003[75]	Placebo + NS vs. NAC + NS	43	Cr ≥1.5 mg/dl at morning of procedure	62-82	6 (14)	72 hours	LOCM (Iopromide, Ioxilan) IA	Oral	A1	H
Marenzi, 2006[78]	Placebo + NS vs. standard-dose NAC + NS vs. high-dose NAC + NS	354	Acute MI, STEMI	62-63	50 (14)	72 hours	LOCM (Iohexol) IA	IV/ Oral	A1	M

Evidence Table E-4. Summary of studies comparing N-acetylcysteine versus placebo or usual care for the prevention of contrast induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	NAC route	Definition of CIN*	Study limitations†
Miner, 2004[83]	Placebo + 0.45% saline vs. high-dose NAC + 0.45% saline	180	Moderate renal impairment	69-71	59 (33)	6 months	LOCM (Iohexol) IA	Oral	A1	H
Ochoa, 2004 [85]	Placebo + NS vs. high-dose NAC + NS	80	Documented chronic renal	70-73	46 (58)	30 days	IOCM (Iodixanol), LOCM (Iohexol), HOCM (Ioxaglate) IA	Oral	A3	H
Oldemeyer, 2003[86]	Placebo + 0.45% saline vs. high-dose NAC + 0.45% saline	96	CrCl <50ml/min, or Cr >1.2 mg/dl	67-86	43 (45)	48 hours	LOCM (Iopamidol) IA	Oral	A3	M
Ozcan, 2007[87]	NS vs. NAC + NS	264	General	69	(25)	2 days	LOCM (Ioxaglate) IA	Oral	A3	L
Poletti, 2007[90]	Hydration + 0.45% saline vs. high-dose NAC + 0.45% saline	100	Cr concentration >106 µmol/L (1.2 mg/dL)	70-73	32 (32)	4 days	LOCM (Iopromide) IV	IV	≥50% increase from CR baseline	L
Rashid, 2004[94]	IV Normal Saline vs IV Normal Saline + Oral NAC	94	Peripheral vascular disease	68-72	34 (36)	7 days	LOCM (iohexol) IA	IV	A3	L
Ratcliffe, 2009[93]	Saline + NS + dextrose vs. high-dose NAC + NS + dextrose	78	Cr >132.6umo/L or CrCl <1.0ml/s, diabetic	64-67	24 (31)	7 days	IOCM (Iodixanol) IA	IV	A1	H
Reinecke, 2007 [95]	NS vs. NAC + NS + glucose	424	Cr >1.3 mg/dl	67-68	73 (17)	553 days	LOCM (Iopromide) IA	Oral	A2	H
Sadat, 2011[96]	NS vs. NAC + NS	40	Cr >1.2 mg/dl or CrCl <60ml/min	75	NR	7 days	LOCM (Iopamidol) IA	Oral	A1	M
Sandhu, 2006[97]	Usual care (no NAC) vs. NAC (hydration NR)	106	General	66-70	40 (38)	48 hours	IOCM (Iodixanol), LOCM (Iopamidol) IA	Oral	A2	M
Sar, 2010[99]	NS vs Oral NAC + IV NS	45	Diabetic	54-60	21 (47)	72 hours	LOCM (Iohexol) IA	Oral	SrCr ≥0.3 mg/dl or ≥20%	
Seyon, 2007[100]	Placebo + 0.45% saline vs. NAC + 0.45% saline	40	Renal dysfunction	75-76	14 (35)	48 hours	Most LOCM, one ICOM, one unknown IA	Oral	A2	H
Shyu, 2002[104]	0.45% saline vs. NAC + 0.45% saline	121	Chronic renal failure with stable Cr concentrations	70	39 (32)	7 days	LOCM (Iopamidol) IA	Oral	A2	L
Tanaka, 2011[105]	Placebo + Ringer's Lactate vs. high-dose NAC + Ringer's Lactate	82	STEMI with PCI	61-63	14 (17)	72 hours	LOCM (Iopamidol) IA	Oral	A1	H

Evidence Table E-4. Summary of studies comparing N-acetylcysteine versus placebo or usual care for the prevention of contrast induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	NAC route	Definition of CIN*	Study limitations†
Tepel, 2000 [106]	Placebo + 0.45% saline vs. NAC + 0.45% saline	83	CR concentration >1.2 mg per deciliter (or CrCl <50 ml per minute)	65-66	36 (43)	6 days	LOCM (Iopamidol) IV	Oral	A2	H
Thayssen, 2014[107]	IV Normal Saline vs IV Normal Saline + oral NAC vs IV Normal Saline + IV NaHCO3 vs IV Normal Saline + oral NAC + IV NaHCO3	715	STEMI	63	165 (23.1)	30 Days	IOCM (Iodixanol) IA	Oral	A1	M
Thiele, 2010[108]	Placebo + NS vs. NAC + NS	251	Acute MI, STEMI	68	80 (32)	6 months	LOCM (Iopromide) IA	IV	A1	M
Traub, 2013[110]	IV Normal Saline vs. IV NAC+IV Normal Saline	399	General	60	237 (59.4)	72 hours	IOCM (Iodixanol) LOCM (Iopamidol and Ioversol) IV	IV	A3	H
Wang, 2008[114]	NS vs. IV NAC + NS	46	General	66-69	19 (41.3)	24 hours	LOCM (Iopromide) IA	IV	NR	
Webb, 2004[115]	Placebo + NS vs. NAC + NS	487	GFR <50 ml/min	70	190 (39)	3 days	LOCM (Ioversol) IA	IV	A1	L
Yeganehkhah, 2014[117]	IV Normal Saline vs. Oral NAC + IV Normal Saline	100	High risk of CIN	59.2	72 (48)	48hrs	LOCM (Iohexol) IA	Oral	A1	H

%=percent; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; CM=contrast media; CrCl=creatinine clearance; Cr=creatinine; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; HOCM=high osmolar contrast media; IA=intrarterial; ICU=intensive care unit; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low-osmolar contrast media; mg/dl=milligram per deciliter; MI=myocardial infarction; ml/min=milliliter per minute; ml/min=milliliter per minute; mmol/l=millimole per liter; N=sample size; NAC=N-acetylcysteine; NR=not reported; NS=normal saline; PCI=percutaneous coronary intervention; STEMI=st elevation myocardial infarction; vs.=versus

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis

Author, year	Measure	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Awal, 2011[10]	Incidence of CIN	Normal Saline	1	24-48 hours	50	6 (12)	p=0.012				
Awal, 2011[10]	Incidence of CIN	NAC	2		50	0 (0)					
Baker, 2003[12]	Incidence of CIN	Normal Saline	1				OR, 0.27 (95% CI: 0.08 to 0.85), p=0.019	96 hours	39	8 (20.5)	Relative Risk: 0.28 (95% CI: 0.08 to 0.98), p=0.045
Baker, 2003[12]	Incidence of CIN	Saline + NAC	2						41	2 (4.9)	
Baranska-Kosakowska, 2007[14]		Hydration	1	NS	57	0					
Baraka-Kosakowska, 2007[14]		NAC	2		55	0					
Burns, 2010[24]	Incidence of CIN	Placebo	1	5 days	21	(14.3); P<0.05 vs nondiabetics within the same drug group (Fisher exact test)	p=0.61				
Burns, 2010[24]	Incidence of CIN	NAC	2		21	(4.8)					
Chousterman, 2011[29]	Incidence of CIN, AKIN serum creatinine definition only	Control	1	48 hours	70	15 (21)	Arm1 vs Arm2 Absolute difference: -13% (95% CI: -24, 1), p=0.033				
Chousterman, 2011[29]	Incidence of CIN, AKIN serum creatinine definition only	NAC	2		70	6 (9)					

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	Interven tion	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Chouster man, 2011[29]	Incidence of CIN, classical CIN definition	Control	1	48 hours	70	15 (21)	Arm1 vs Arm2 Absolute difference: -7% (95% CI: -20, 6), p=0.27				
Chouster man, 2011[29]	Incidence of CIN, classical CIN definition	NAC	2		70	10 (14)					
Chouster man, 2011[29]	Incidence of CIN, whole AKIN definition	Control	1	48 hours	70	22 (31)	Arm1 vs Arm2 Absolute difference: 3% (95% CI: -21, 18), p=0.72				
Chouster man, 2011[29]	Incidence of CIN, whole AKIN definition	NAC	2		70	24 (34)					
Chouster man, 2013[30]	(AKIN definition) increase in serum creatinine of at least 0.3 mg/dLor increase to more than or equal to 50% from baseline and/or oliguria of less than 0.5 mL/kg per hour for more than 6 hours	Saline	1	48 hours	70	22 (31)	Absolute diff (95%), +3% (95% CI: -12 to 18), p=.72				

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	Interven tion	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Chouster man, 2013[30]	(AKIN definition) increase in serum creatinine of at least 0.3 mg/dLor increase to more than or equal to 50% from baseline and/or oliguria of less than 0.5 mL/kg per hour for more than 6 hours	NAC	2		70	24 (34)					
Chouster man, 2013[30]	an increase in plasma creatinine of 0.3 mg/dl or more from baseline	Saline	1	48 hours	70	15 (21)	Absolute diff (95%), -7% (95% CI: -20 to 6), p=0.27				
Chouster man, 2013[30]	an increase in plasma creatinine of 0.3 mg/dl or more from baseline	Saline	1	48 hours	70	15 (21)	Absolute diff (95%), -13% (95% CI: -24 to -1), p=0.033				
Chouster man, 2013[30]	an increase in plasma creatinine of 0.3 mg/dl or more from baseline	NAC	2		70	10 (14)					
Chouster man, 2013[30] (continued)	an increase in plasma creatinine of 0.3 mg/dl or more from baseline	NAC	2		70	6 (9)					

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Fung, 2004[37]	>25% SCr or >0.5 mg/dl	Hydration	1	during study period (within 48 hours post-procedure)		6 (13.3)	p=0.8				
Fung, 2004[37]	>25% SCr or >0.5 mg/dl	Hydration + NAC	2			8 (17.4)					
Kim, 2010[60]	an increase in serum creatinine concentration of at least 0.5 mg/dL or a greater than 25% within 48 h of contrast exposure	control	1	48 hours	86	7 (8.1)	p=NS				
Kim, 2010[60]	an increase in serum creatinine concentration of at least 0.5 mg/dL or a greater than 25% within 48 h of contrast exposure	NAC	2		80	3 (3.8)					

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Koc, 2012[63]	baseline SCr ≥ 25% and/or an absolute increase in SCr of ≥ 0.5 mg/dL 48 hours after the procedure	Normal Saline	1	48 hours	60	6 (10)	All arms p=.012				
Koc, 2012[63]	baseline SCr ≥ 25% and/or an absolute increase in SCr of ≥ 0.5 mg/dL 48 hours after the procedure	NAC + high-dose saline	2		80	2 (2.5)					
Kumar, 2014[67]	Incidence of CIN	IV NS	1	5 days	90	31	NR				
Kumar, 2014[67]	Incidence of CIN	Oral NAC + IV NS	2		90	18	NR				
Lawlor, 2007[68]	>25% SCr or >0.5 mg/dl	Placebo	1	48 hours	25	2 (8)	p=0.99				
Lawlor, 2007[68] (continued)	>25% SCr or >0.5 mg/dl	NAC+IV hydration	2		25	2 (8)					
Lawlor, 2007[68]	>25% SCr or >0.5 mg/dl	NAC+Oral hydration	3		28	2 (7)					
Sandhu, 2006[97]	>25% SCr or >0.5 mg/dl	Control	1	48 hours	53	0					
Sandhu, 2006[97]	>25% SCr or >0.5 mg/dl	NAC	2		53	3					

Evidence Table E-5. Contrast induced nephropathy outcomes in studies comparing of N-acetylcysteine versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comp-rison* statistics at time point 1	Time Point 2	Time point 2 N ana-lyzed	n (%) with out-come at time-point 2	Comp-rison statist-cs at time point 2
Webb, 2004[115]	> 44 umol/l in crease in serum creatinine, per protocol analysis	Placebo	1	2-8 days	204	(5.9)	p=0.69				
Webb, 2004[115]	> 44 umol/l in crease in serum creatinine, per protocol analysis	NAC	2		194	(7.2)					
Yeganeh khah, 2014[117]	Incidence of CIN	IV NS	1	48 hrs	50	7	P=0.944				
Yeganeh khah, 2014[117]		Oral NAC + IV NS	2		50	6					

%=percent; A1=arm 1; A2=arm 2; A3=arm 3; AKIN=Acute Kidney Injury Network; CECT= contrast enhanced computed tomography; CI=confidence interval; CIN=contrast induced nephropathy; Cr=creatinine; GFR=glomerular filtration rate; H=hour; IA=intrarterial; IV=intravenous; Mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NR=not reported; NS=non-signficant; OR=odds ratio; P=p-value; RR=relative risk; SCr=serum creatinine; SG=subgroups; Umol/l=micromole per liter

Evidence Table E-6. Changes in serum creatinine outcomes in studies comparing of N-acetylcysteine versus placebo or usual care

Author year	Measure	SG	Interven-tions	Arm	Base-line N anal-yzed	Mean base-line value (SD)	Time point 1	Time point 1 N anal-yzed	Mean (SD)	Comp-arison* statistics at time point 1	Time point 2	Time point 2 N anal-yzed	Mean (SD)	Comp-arison statistics at time point 2	Time Point 3	Time point 3, N analyz ed	Mean (SD)	Comp-arison statistics at time point 3
Buyukhatipoglu, 2010[25]	Change in serum creatinine, regression analysis	Contrast amount	Control	1			24 hours			Beta coefficient: 0.213, p=0.712 T-test: 0.371								
Buyukhatipoglu, 2010[25]	Change in serum creatinine, regression analysis	Contrast amount	NAC + saline	2														
Buyukhatipoglu, 2010[25]	Change in serum creatinine, regression analysis	NAC use	Control	1			24 hours			Beta-coefficient: 0.305, p=0.068 t-test: 1.877								
Buyukhatipoglu, 2010[25]	Change in serum creatinine, regression analysis	NAC use	NAC + saline	2														
Heng, 2008[122]	Change in serum creatinine, umol/l, from baseline		Placebo	1			2 days	32	-3 (28)	p=0.84								
Heng, 2008[122]	Change in serum creatinine, umol/l, from baseline		NAC	2				28	-2 (25)									

Evidence Table E-6. Changes in serum creatinine outcomes in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author year	Measure	SG	Interven-tions	Arm	Base-line N anal-yzed	Mean base-line value (SD)	Time point 1	Time point 1 N anal-yzed	Mean (SD)	Comp-arison* statistics at time point 1	Time point 2	Time point 2 N anal-yzed	Mean (SD)	Comp-arison statistics at time point 2	Time Point 3	Time point 3, N analyz ed	Mean (SD)	Comp-arison statistics at time point 3
Kumar, 2014[67]	Change in serum creatinine levels		IV NS	1	90		1-3 days	90	Iohexanol: 0.15 (0.06) Iodixanol: 0.18 (0.01)		3-5 days	90	Iohexanol: -0.22 (0.10) Iodixanol: -0.10 (0.02)					
Kumar, 2014[67]	Change in serum creatinine levels		Oral NAC + IV NS	2	90			90	Iohexanol: -0.10 (0.06) Iodixanol: 0.09 (0.01)	P=0.01		90	Iohexanol: --0.12 (0.06) Iodixanol: -0.08 (0.01)	P=0.01				
Sar, 2010[99]	mg/dL		Saline	1	20	0.81 (0.17)	48 hours	20	0.94 (0.16)	p=0.03								
Sar, 2010[99]	mg/dL		Saline + NAC	2	25	0.83 (0.15)		25	0.79 (0.21)									
Staniloae, 2009[123]			no NAC	1	246	1.47 (0.36)	48-72 hours	246	1.57 (0.44)	p=0.12								
Staniloae, 2009[123]			NAC	2	168	1.43 (0.40)		168	1.51 (0.42)									

Evidence Table E-6. Changes in serum creatinine outcomes in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author year	Measure	SG	Interven-tions	Arm	Base-line N anal-yzed	Mean base-line value (SD)	Time point 1	Time point 1 N anal-yzed	Mean (SD)	Comp-arison* statistics at time point 1	Time point 2	Time point 2 N anal-yzed	Mean (SD)	Comp-arison statistics at time point 2	Time Point 3	Time point 3, N analyz ed	Mean (SD)	Comp-arison statistics at time point 3
Traub, 2013[110]	Change in SCr		IV Normal Saline	1			48-72 hours	172	-0.025 (0.227) Median: 0 (Range: -1.0-1.3)	Mean Difference: 0.025 (95% CI: -0.025-0.075) p=NR								
Traub, 2013[110]	Change in SCr		IV NAC	2				185	-0.05 (0.252) Median: 0 (Range: -1.1-1.7)									
Traub, 2013[110]	Percentage change		IV Normal Saline	1			48-72 hours	172	-1.3 (19.8) (-58.9 to 81.3)	Mean difference: 1.5 (95% CI: -3.0-6.0) p=NR								
Traub, 2013[110]	Percentage change		IV NAC	2				185	-2.7 (23.4) (-61.1 to 154.5)									

Evidence Table E-6. Changes in serum creatinine outcomes in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author year	Measure	SG	Interventions	Arm	Baseline N analyzed	Mean baseline value (SD)	Time point 1	Time point 1 N analyzed	Mean (SD)	Comparison* statistics at time point 1	Time point 2	Time point 2 N analyzed	Mean (SD)	Comparison statistics at time point 2	Time Point 3	Time point 3, N analyzed	Mean (SD)	Comparison statistics at time point 3
Wang, 2008[114]	Serum creatinine levels at baseline and follow-up		Saline	1	23	1.18 (0.50)	24 hours	23	1.09 (0.50)	p=0.27								
Wang, 2008[114]	Serum creatinine levels at baseline and follow-up		Saline + NAC	2	23	1.48 (0.81)		23	1.30 (0.74)									
Yeganehkhah, 2014[117]	Serum Creatinine levels		IV NS	1	50	1.08 (0.32)	48	50	1.13 (0.28)	0.039								
Yeganehkhah, 2014[117]	Serum Creatinine levels		Oral NAC + IV NS	2	50	1.17(0.43)		50	1.11 (0.35)	0.195								

CI=confidence interval; H=hours; Hrs=hours; IQR=interquartile range; IV=intravenous; LVEF=left ventricular ejection fraction; Mg/dl=milligram per deciliter; Mg=milligram; Ml=milliliter; N=sample size; NAC=N-acetylcysteine; NR=not reported; NS=non-significant; NS=non-significant; P=p-value; SCr=serum creatinine; SG=subgroups; Umol/l=micromole per liter; V=versus; Yrs=years;

Evidence Table E-7. GFR levels in studies comparing of N-acetylcysteine versus placebo or usual care

Author year	Measure	SG	Interven-tions	Arm	Base-line N analyzed	Mean base-line value (SD)	Time point 1	Time point 1 N analyzed	Mean (SD)	Comparison * statistics at time point 1	Time point 2	Time point 2 N analyzed	Mean (SD)	Comparison statistics at time point 2
Erturk, 2014[34]	ml/min/1.73 m^2		IV normal saline	1	103	44 (10)	24 hours	103	47 (13)	p= 0.423	48 hours	103	45 (13)	p=0.672
Erturk, 2014[34]	ml/min/1.73 m^2		Oral NAC + IV normal saline	2	102	46 (9)		102	49 (13)			102	46 (13)	
Erturk, 2014[34]	ml/min/1.73 m^2		IV NAC + IV normal saline	3	102	45 (9)		102	46 (13)			102	46 (13)	
Kama, 2014[54]	GFR, units not specified		IV Normal Saline	1	35	49.7 (95% CI: 39.2-60.3)	48-72 hours	35	39 (95% CI: 43.8-64.4)	p=0.49				
Kama, 2014[54]	GFR, units not specified		IV NAC in Normal Saline	2	36	44 (95 % CI: 33.5-54.4)		36	36 (95% CI: 35.9-57.2)					
Kama, 2014[54]	GFR, units not specified		IV NaHCO3 in Normal Saline	3	36	43.5 (95% CI: 33.5-53.5)		36	35 (95% CI: 36.2-61.6)					
Sar, 2010[99]	mL/min		Saline	1	20	97.8 (28.6)	48 hours	20	99.4 (35.7)	p=0.021				
Sar, 2010[99]	mL/min		Saline + NAC	2	25	90.9 (25.1)		25	90.8 (25.0)					
Staniloae, 2009[123]	Mean change in eGFR		no NAC	1			45-120 hours	246	-3.32 (8.1)	p=0.51				
Staniloae, 2009[123]	Mean change in eGFR		NAC	2				168	-2.79 (7.8)					

Evidence Table E-7. GFR levels in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author year	Measure	SG	Interven-tions	Arm	Base-line N analyzed	Mean base-line value (SD)	Time point 1	Time point 1 N analyzed	Mean (SD)	Comparison* statistics at time point 1	Time point 2	Time point 2 N analyzed	Mean (SD)	Comparison statistics at time point 2
Wang, 2008[114]	eGFR measured at baseline and after procedure		Saline	1	23	57.97 (26.38)	24 hours	23	63.00 (29.27)	p=0.71				
Wang, 2008[114]	eGFR measured at baseline and after procedure		Saline + NAC	2	23	59.54 (47.13)		23	68.10 (57.65)					

eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; N=sample size; NAC=N-acetylcysteine; P=p-value; SD=standard deviation; SG=subgroups

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
ACT, 2011[3]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	At 30 days Arm1: 24/1135 (2.1) Arm2: 23/1171 (2.0) RR 0.97 (95% CI: 0.54-1.73); P=0.92	At 30 days Arm1: 3/1135 (0.3) Arm2: 3/1171 (0.3) RR 0.87 (95% CI: 0.17-4.35); P=0.86	NR	NR
Alioglu, 2013[6]	Arm 1: 0.45% saline Arm 2: NAC + 0.45% saline	NR	NR	NR	NR
Allaqaband, 2002[7]	Arm1: 0.45% saline Arm2: 0.45% saline + NAC Arm3: 0.45% saline + fenoldopam	NR	Time point: NR, 20 who developed CIN needed hemodialysis, no other details	NR	NR
Amini, 2009[8]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	NR	NR	NR	NR
Aslanger, 2012[9]	Arm 1: Placebo+ NS Arm 2: high-dose NAC+ NS	NR	NR	NR	NR
Awal, 2011[10]	Arm 1: NS Arm 2: NAC+ NS	NR	NR	NR	NR
Azmus, 2005[11]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	At 48 hours: 6/201 (3.0) Arm2: 5/196 (2.5); P=1.0	At 48 hours Arm1: 1/201 (0.5) Arm2: 1/196 (0.5); P=1.0	NR	NR
Baker, 2003[12]	Arm 1: NS Arm 2: NAC+ NS	NR	At 96 hours Arm1: 0/39 (0) Arm2: 0/41 (0); P=NR	NR	Pulmonary edema at 96 hours Arm1: 2/39 Arm2: 2/41; P=NR
Baranska-Kosakowska, 2007[14]	Arm1: NS Arm2: IV NAC + NS	NR	NR	NR	NR
Baskurt, 2009[13]	Arm1: NS Arm2: NS + NAC Arm3: NS + NAC + theophylline	NR	NR	NR	Major adverse cardiac events at 48 hours Arm1: 0/42 (0) Arm2: 0/73 (0) Arm3: 0/72 (0); P=NR
Boccalandro, 2003[17]	Arm 1: Placebo + 0.45% saline Arm 2: NAC + 0.45% saline	NR	NR	NR	NR
Briguori, 2002[21]	Arm 1: 0.45% saline Arm 2: NAC + 0.45% saline	NR	At 48 hours Arm1: 1/91 (1.1) Arm2: 0/92 (0); P=NR	NR	NR
Brueck, 2013[23]	Arm1: placebo + NS Arm2: IV-NAC+ NS Arm3: IA-NAC+ NS	NR	NR	NR	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Burns, 2010[24]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	At 5 days Arm1: 9/21 (42.9) Arm2: 6/21 (28.6); P=0.52	At 5 days Arm1: 0/21 (0) Arm2: 0/21 (0); P=NR	All patients (ICU) Arm1: 13.1 (7.9) Arm2: 24.4 (23.5); P=0.47 Survivors (ICU) Arm1: 13.7 (7.3) Arm2: 25.0 (24.9); P=0.65 All patients (hospital stay) Arm1: 41.5 (42.6) Arm2: 50.7 (23.6); P=0.71 Survivors (hospital stay) Arm1: 45.8 (27.8) Arm2: 57.2 (60.6); P=0.68	NR
Buyukhatipoglu, 2010[25]	Arm1: NS Arm2: IV NAC + NS	NR	NR	NR	NR
Carbonell, 2007[26]	Arm 1: Placebo + 0.45% saline Arm 2: NAC + 0.45% saline	Time point: NR Arm1: 5/109 (4.6) Arm2: 3/107 (2.8); P=NR	NR	Coronary unit stay Arm1: median 4 (2-37) Arm2: median 4.5 (2-24); P=NR	NR
Carbonell, 2010[27]	Arm 1: Placebo + 0.45% saline Arm 2: NAC + 0.45% saline	Coronary unit Time point: short-term Arm1: 2/42 (4.2) Arm2: 3/39 (7.7) OR 0.20 (95% CI: 0.04-0.97) P=0.18 In-hospital Time point: short-term Arm1: 7/42 (16.7) Arm2: 4/39 (10.3); P=0.65 Long-term Arm1: 9/42 (21.4) Arm2: 6/39 (15.4); P=0.67	At 12 months Arm1: 1/42 (2.0) Arm2: 0/39 (0); P=0.15	Coronary unit stay Arm1: median 4 (2-27) Arm2: median 5 (1-20); P=0.70 Hospital Arm1: median 10 (2-76) Arm2: median 10 (1-42); P=0.20	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Castini, 2010[28]	Arm1: NS Arm2: NS + NAC Arm3: NaHCO3	NR	NR	NR	NR
Chousterman, 2011[29]	Arm 1: NS Arm 2: NAC + NS	NR	NR	NR	NR
Chousterman, 2013[30]	Arm 1: NS Arm 2: NAC + NS	NR	Time point: NR Arm1: 5/54 (9) Arm2: 7/62 (11); P=NR	NR	NR
Demir, 2008[31]	Arm1:NS Arm2: NAC + NS Arm3: misopriatol + NS Arm4: theophylline + NS Arm5: nifedipine + NS	NR	NR	NR	NR
Durham, 2002[32]	Arm 1: 0.45% Saline Arm 2: high-dose NAC + 0.45% saline	NR	Whole population: 2/79 (2.4%) P=NR	NR	NR
Erturk, 2014[34]	Arm1: IV Normal Saline Arm2: Oral NAC + IV Normal Saline Arm3: IV NAC + IV Normal Saline	30 days Arm1: 3/103 (2.9) Arm2: 0/102 (0) Arm3: 1/102 (1) p=0.173 1 year Arm1: 7/103 (6.8) Arm2: 8/102 (7.8) Arm3: 12/102 (11.8) p=0.417	Dialysis at 30 days Arm1: 2/103 (1.9) Arm2: 0/102 (0) Arm3: 0/102 (0) p=0.136 Dialysis at 1 year Arm1: 3/103 (2.9) Arm2: 1/102 (1) Arm3: 0/102 (0) p=0.173	NR	NR
Ferrario, 2009[35]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	At 72 hours Arm1: 0/101 (0) Arm2: 0/99 (0); P=NR	At 72 hours Arm1: 0/101 (0) Arm2: 0/99 (0); P=NR	NR	NR
Fung, 2004[37]	Arm 1: NS Arm 2: NAC+ NS	NR	Temporary dialysis therapy for acute renal failure Time point: NR Arm1: 0/45 (0) Arm2: 0/46 (0); P=NR	NR	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Goldenberg, 2004[38]	Arm 1: Placebo + 0.45% Saline Arm 2: NAC + 0.45% saline	NR	NR	NR	Overt congestive heart failure Time point: NR Arm1: 1/39 (3) Arm2: 1/41 (2); P=74
Gomes, 2005[39]	Arm 1: Placebo+ NS Arm 2: NAC+ NS	Time point: NR Arm1: 2/79 (2.5) Arm2: 5/77 (6.5); P=0.42	Time point: NR Arm1: 0/79 (0) Arm2: 2/77 (2.6); P=0.24	NR	NR
Gulel, 2005[41]	Arm 1: NS Arm 2: NAC+ NS	NR	NR	NR	NR
Gunebakmaz, 2012[42]	Arm1: NS Arm2: NS + nebivolol Arm3: NAC + NS	NR	NR	NR	NR
Holscher, 2008[46]	Arm1: NS + glucose Arm2: NS + dialysis + glucose Arm3: NS + NAC + glucose	NR	NR	NR	NR
Hsu, 2007[47]	Arm 1: NS Arm 2: NAC+ NS	NR	Time point: NR Arm1: 0/9 (0) Arm2: 0/11 (0); P=NR	Arm1: 8.1 (4.1) Arm2: 5.2 (1.5); P=0.04	Acute coronary syndrome or acute congestive heart failure Time point: NR Arm1: 0/9 (0) Arm2: 0/11 (0); P=NR
Hsu, 2012[48]	Arm 1: NS Arm 2: NAC+ NS	Time point: NR Arm1: 13/103 (12.6) Arm2: 8/106 (7.5) OR 0.57 (95% CI: 0.224-1.427) P=NR	Time point: NR Arm1: 0/103 (0) Arm2: 0/106 (0); P=NR	NR	NR
Izani Wan Mohamed, 2008[49]	Arm 1: 0.45% Saline Arm 2: NAC + 0.45% saline	NR	Patients who developed CIN at 48 hours Arm1: 0/6 (0) Arm2: 0/2 (0); P=NR	NR	NR
Jaffery, 2012[50]	Arm 1: NS Arm 2: high-dose NAC+ NS	Time point: short-term Arm1: 1/192 (0.5) Arm2: 1/206 (0.5); P=1.0 At 30 days Arm1: 3/192 (1.6) Arm2: 3/206 (1.3); P=1.0	NR	Arm1: 3.6 (3.3) Arm2: 3.2 (2.6); P=0.13	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Kama, 2014[54]	Arm1: IV Normal Saline Arm2: IV NAC in Normal Saline Arm3: IV NaHCO3 in Normal Saline	NR	Need for RRT 1 month Arm1: 0 (0) Arm2: 3 (803) Arm3: 2 (5.6) p=NR	NR	NR
Kay, 2003[57]	Arm 1: Placebo + NS Arm 2: NAC+ NS	NR	NR	Arm1: 3.9 (2.0) Arm2: 3.4 (0.9) RR 0.52 (95% CI: 0.08-0.96) P=0.02	NR
Kefer, 2003[58]	Arm 1: Placebo + dextrose Arm 2: high-dose NAC + dextrose	NR	NR	NR	NR
Khalili, 2006[59]	Arm 1: NS Arm 2: NAC+ NS	NR	NR	NR	NR
Kim, 2010[60]	Arm 1: NS Arm 2: high-dose NAC+ NS	NR	NR	NR	NR
Kimmel, 2008[61]	Arm 1: Placebo + 0.45% Saline Arm 2: NAC + 0.45% saline	NR	NR	NR	NR
Kinbara, 2010[62]	Arm1: NS Arm2: NS + aminophylline Arm3: NS + high-dose NAC	NR	NR	NR	NR
Koc, 2012[63]	Arm1: Standard NS Arm2: IV NAC + High dose NS Arm3: High dose NS	NR	NR	NR	NR
Kotlyar, 2005[66]	Arm1: NS Arm2: NAC 300mg + NS Arm3: NAC 600mg + NS	NR	Chronic reductions in renal function at 30 days Arm1: 2/19 (11) Arm2: 4/20 (20) Arm3: 2/21 (10); P=0.66	NR	NR
Kumar, 2014[67]	Arm 1: IV NS Arm 2: Oral NAC + IV NS	NR	NR	NR	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Lawlor, 2007[68]	Arm1: Placebo + IV NS Arm2: IV hydration + oral NAC Arm3: Oral hydration + oral NAC	NR	Need for Dialysis At 48 hours Arm1: 0 (0) Arm2: 0 (0) Arm3: 0 (0) p=NR	NR	NR
MacNeill, 2003[75]	Arm 1: Placebo + NS Arm 2: NAC+ NS	NR	NR	NR	NR
Marenzi, 2006[78]	Arm1: Placebo + NS Arm2: NAC + NS Arm3: High-dose NAC + NS	Time point: NR Arm1: 13/119 (11) Arm2: 5/115 (4) Arm3: 3/118 (3); P=0.007	Time point: NR Arm1: 6/119 (5) Arm2: 2/115 (2) Arm3: 1/118 (1); P=0.14	NR	NR
Miner, 2004[83]	Arm 1: Placebo + 0.45% Saline Arm 2: High-dose NAC + 0.45% saline	In-hospital Time point: NR Arm1: 2 Arm2: 0; P=NR Long-term Time point: NR Arm1: 3 (3.5) Arm2: 4 (4); P=NR	In-hospital Time point: NR Arm1: 0 Arm2: 1; P=NR Time point: NR Arm1: 1 Arm2: 1; P=NR	NR	Non-fatal MI, in-hospital Time point: NR Arm1: 1 Arm2: 6; P=0.14 Non-fatal MI, long-term Time point: NR Arm1: 4 Arm2: 6; P=NR
Ochoa, 2004 [85]	Arm 1: Placebo + NS Arm 2: NAC+ NS	NR	NR	NR	NR
Oldemeyer, 2003[86]	Arm 1: Placebo + 0.45% Saline Arm 2: High-dose NAC + 0.45% saline	NR	At 48 hours Arm1: 0/47 (0) Arm2: 0/48 (0); P=NR	Arm1: 4.9 (4.0) Arm2: 4.8 (3.8); P=NR	NR
Ozcan, 2007[87]	Arm1: NS Arm2: NS + NAC Arm3: bicarbonate	NR	At 48 hours Arm1: 1/88 (1.14) Arm2: 0/88 (0) Arm3: 1/88 (1.14); P=NR	NR	Incidence of congestive heart failure at 48 hours Arm1: 0/88 (0) Arm2: 0/88 (0) Arm3: 0/88 (0); P=NR
Poletti, 2007[90]	Arm 1: NS + 0.45% Saline Arm 2: High-dose NAC + 0.45% saline	NR	NR	NR	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Rashid, 2004[94]	Arm1: IV Normal Saline Arm2: IV Normal Saline + Oral NAC	At 7 days Arm1: 0/48 (0) Arm2: 1/46 (2.2) p=NR	At 7 days Arm1: 1/48 (2.1) Arm2: 0/46 (0) p=NR	NR	NR
Ratcliffe, 2009[93]	Arm1: NS Arm2: NS + high-dose NAC Arm3: NaHCO3 Arm4: NaHCO3 + NAC	NR	NR	NR	NR
Reinecke, 2007 [95]	Arm1: NS + glucose Arm2: NS+ dialysis + glucose Arm3: NS+ NAC + glucose	In hospital Arm1: 1/NR (0.7) Arm2: 3/NR (2.2) Arm3: 1/NR (0.7); P=0.427 30-day Arm1: 3/NR (2.2) Arm2: 3/NR (2.2) Arm3: 1/NR (0.7); P=0.540 Months NR Arm1: 9.7 Arm2: 13.1 Arm3: 9.9; P=0.582	In-hospital Time point: NR Arm1: 1/NR (0.7) Arm2: 22/133 (1.5) Arm3: 1/NR (0.7); P=0.762	NR	NR
Sadat, 2011[96]	Arm1: NS Arm2: NS + NAC	NR	NR	NR	NR
Sandhu, 2006[97]	Arm 1: No treatment Arm 2: NAC	NR	NR	NR	NR
Sar, 2010[99]	Arm1: NS Arm2: Oral NAC + IV NS	NR	NR	NR	NR
Seyon, 2007[100]	Arm 1: Placebo + 0.45% Saline Arm 2: NAC + 0.45% saline	NR	NR	NR	NR
Shyu, 2002[104]	Arm 1: 0.45% Saline Arm 2: NAC + 0.45% saline	NR	Time point: NR Arm1: 1 Arm2: 0; P=NR	NR	NR
Tanaka, 2011[105]	Arm 1: Placebo + Ringer's Lactate Arm 2: High-dose NAC + Ringer's Lactate	NR	NR	Arm1: 20.8 (8.9) Arm2: 18.7 (5.6); P=0.22	NR
Tepel, 2000 [106]	Arm 1: 0.45% Saline Arm 2: NAC + 0.45% saline	NR	NR	NR	NR

Evidence Table E-8. Summary of other outcomes reported in studies comparing N-acetylcysteine and placebo or usual care for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Thayssen, 2014[107]	Arm1: IV Normal Saline Arm2: IV Normal Saline + oral NAC Arm3: IV Normal Saline + IV NaHCO3 Arm4: IV Normal Saline + oral NAC + IV NaHCO3	NR	30 Days Arm1: 0/181 (0) Arm2: 0/176 (0) Arm3: 0/181 (0) Arm3: 0/177 (0) p=NR	NR	Cardiac major events, composite (cardiac death, myocardial infarction, target vessel revascularization) Arm1: 4/181 (2.2) Arm2: 0/176 (0) Arm3: 6/181 (3.6) Arm3: 3/177 (1.7) p=0.13
Thiele, 2010[108]	Arm 1: Placebo + NS Arm 2: NAC+ NS	At 6 months Arm1: 12/125 Arm2: 12/126; P=NR	NR	NR	Non-fatal reinfarctions At 6 months Arm1: 4/125 (3.2) Arm2: 3/126 (2.4); P=NR New congestive heart failure at 6 months Arm1: 7 (5.6) Arm2: 11 (8.7); P=NR
Traub, 2013[110]	Arm1: IV Normal Saline Arm2: IV NAC	NR	NR	NR	NR
Wang, 2008[114]	Arm1: NS Arm2: IV NAC + NS	NR	NR	NR	NR
Webb, 2004[115]	Arm 1: Placebo + NS Arm 2: NAC+ NS	At 8 days Arm1: 5/227 Arm2: 7/220; P=NR At >8 days Arm1: 4/227 Arm2: 3/220; P=NR	At 2-8 days Arm1: 0/227 Arm2: 0/220; P=NR	NR	NR
Yeganehkhah, 2014[117]	Arm 1: IV NS Arm 2: Oral NAC + IV NS	NR	NR	NR	NR

%=percent; ACT=Acetylcysteine for Contrast-Induced Nephropathy Trial; CI=confidence interval; CIN=contrast induced nephropathy; MI=myocardial infarction; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; NR=not reported; OR=odds ratio; P=p-value; RR=risk ratio; RRT=renal replacement therapy

* n/N refers to number of events divided by number at risk.

Evidence Table E-9. Adverse events in studies comparing of N-acetylcysteine versus placebo or usual care

Author, Year	Adverse events
Allaqaband,2002[7]	Other: Hypotension Fenoldopam reaction. Definition not reported
Azmus, 2005[11]	Other: Nausea: 3 cases placebo 7 cases NAC Vomitting: 1 case placebo 2 cases NAC Epigastric pain: 1 case placebo 1 case NAC
Baker,2003[12]	Other: Allergic reaction Itching, flushing or transitory rash in 14% of patients on NAC
Carbonell, 2007[26]	no patients presented AEs
Carbonell,2010[27]	No patients presented side effects
Castini, 2010[28]	only reported acute renal failure (necessitating HD, ultrafiltration or peritoneal dialysis never occurred.
Erturk, 2014[34]	NR
Fung, 2004[37]	Anaphalaxis: No patient in the NAC group developed an allergic reaction or other adverse event that necessitated withdrawal of NAC. Other: , No patient in the NAC group developed an adverse event that necessitated withdrawal of NAC
Goldenberg, 2004[38]	Heart failure: 2 cases of Congestive heart failure-one in each group Anaphalaxis Other: Transient hypotension, 1 case in the acetylcysteine group,
Gulel, 2005[41]	Other: GI disturbances, 3 pts in control (12%) 4 pts in NAC group (16%) p>0.05,
Heng, 2008[122]	Heart failure: 1 in NAC group Anaphalaxis Other: diarrrhea, 1 in NAC group 2 in placebo group, dialysis, 0 in both groups, , some adverse events were also entered as outcomes
Hsu, 2007[47]	Other: Adverse events after NAC administration, None
Izani Wan Mohamed, 2008[49]	Other: mild gastrointestinal upset and nausea, 2 (4%) patients in Arm 2. Arm 1, one patient developed nausea only, ,
Jaffery, 2012[50]	Other: composite events: in-hospital mortality, mechanical ventilation and acute renal failure requiring dialysis. 2 (1%) Control 3 (1.5%) NAC p=1 adverse event during IV NAC administration
Kama, 2014[54]	No contrast or treatment induced adverse events were detected during emergency department care
Kimmel, 2008[61]	Other: Diarrhoea, Diarrhoea in Zinc group
Kumar, 2014[67]	NR
MacNeill, , 2003[75]	Other: , "Acetylcysteine was well tolerated with no adverse events recorded."
Marenzi, 2006[78]	Other: Cardiopulmonary resuscitation, ventricular tachycardia, or ventricular fibrillation High-rate atrial fibrillation other High-degree conduction disturbances, Cardiogenic shock requiring intraaortic balloon counterpulsation,Acute pulmonary edema requiring mechanical ventilation listed under in-hospital complications

Evidence Table E-9. Adverse events in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author, Year	Adverse events
Miner, 2004[83]	Other: profound thrombocytopenia, Profound thrombocytopenia platelet count 20,000 platelets/mL.NAC=2 Placebo=0 p=ns, blood transfusion, NAC=1 Placebo=2 p=NS other adverse events are our outcomes of intetrest
Ochoa, 2004[85]	Other: Procedurerelated hypotension requiring vasopressors and/or intraaortic balloon counterpulsation, 4 (11%) patients in Arm 2, and in 7 (16%) patients in Arm 1(P = 0.45, Nausea, 1 patient in Arm 1, Serious adverse effects, None
Oldemeyer, 2003[86]	Other: General symptoms, Placebo 0 NAC 8: GI symptoms 6 - headache 1- chest tightness 1,
Ozcan, 2007[87]	No AES related to tx
Rashid, 2004[94]	No patient present any AE due to NAC
Ratcliffe, 2009[93]	Other: Serious adverse events, No serious adverse events from any of the medications given or from the procedure itself,
Reinecke,2007[95]	adverse events reported as secondary outcome.
Tanaka, 2011[105]	Heart failure: Placebo 7/38NAC 4/38p NS Anaphalaxis: 1 pt in the NAC arm had vomitting
Tepel, 2000[106]	Other: GI discomfort-temporary 7% acetylcysteine 12% control group dizziness 10% acetylcysteine 7% control group dialysis 0
Thayssen, 2014[107]	Within 3 days: 3 (0.3%) patients had a target lesion revascularization, 4 (0.6%) had a target vessel revascularization. 11 (1.5%) had a new angiogram for a clinical reason without intervention 9 (1.3%)patients had a nonculprit artery PCI. Within 30 days: 7 (1.0%) patients had a target lesion revascularization, 11 (1.5%) had a target vessel revascularization. 20 (2.8%) had a new angiogram for a clinical reason without intervention, 24 (3.3%) patients had a nonculprit artery PCI.

Evidence Table9. Adverse events in studies comparing of N-acetylcysteine versus placebo or usual care (continued)

Author, Year	Adverse events
Traub, 2013[110]	Itching Arm 1: 2 (1.0) Arm2: 1 Flushing Arm 1: 3 (1.5) Arm 2: 3 (1.5) Rash Arm1: 0 Arm2: 1 (0.5) Hypotension Arm1: 0 Arm2: 0 Wheezing Arm1: 1 (0.5) Arm2: 0 Nausea Arm1:4 (2.0) Arm2:4 (2.0) Vomiting Arm1: 3 (1.5) Arm2:1 (0.5)
Webb, 2004[115]	reported on death and need for dialysis
Yeganehkhah, 2014[117]	NR

%=percent; AE=adverse event; GI=gastro-intestinal; HD=hemodialysis; IV=intravenous; NAC=N-acetylcysteine; NR=not reported; NS=non-significant;

Evidence Table E-10. Summary of studies comparing IV sodium bicarbonate versus IV saline for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population included	Age, Range of means§	Sex, n female (%)‡	Mean followup	CM Route*	Definition of CIN*	Study limitations†
Beyazal, 2014[15]	IV 0.9% Normal Saline vs. IV NaHCO3 + 5% dextrose vs. IV 0.9% Normal Saline + Diltiazem	60	Serum creatinine values between 1.1 and 3.1 mg/dl	62.7	27 (45)	7 months	LOCM (Iohexol) IV	A3	H
Boucek, 2013[19]	IV hypertonic saline vs. IV NaHCO3	120	Diabetes	63-67	30 (25)	2 days	LOCM IA or IV	A3	L
Brar, 2008[20]	IV normal saline vs. IV NaHCO3	323	Stable renal disease	65-76	128 (39)	6 months	LOCM (Ioxilan) IA	A2	L
Castini, 2010[28]	IV normal saline vs. IV NaHCO3 + dextrose	156	General	70-72	19 (5)	5 days	IOCM IA	A1	M
Gomes, 2012[40]	IV normal saline vs. IV NaHCO3 + dextrose	301	CR >1.2 mg/dl, GFR, <50 ml/min	64-64	83 (27)	48 hours	LOCM (Ioxaglate) IA	A2	H
Kama, 2014[54]	IV Normal Saline vs IV NAC in Normal Saline vs IV NaHCO3 in Normal Saline	107	High risk of CIN, using Mehran score (>5 points)	71	48 (45)	1 month	LOCM (Iohexol) IA or IV	A3	M
Koc, 2013[64]	IV normal saline vs. IV NaHCO3	195	Diabetic	40-53	93 (47)	2 days	LOCM (Iohexol) IA	A3	M
Kooiman, 2014[65]	IV Normal Saline vs IV NaHCO3 + IV Normal Saline	548	CKD (eGFR <60ml/min/1.73m^2)	72	227 (41.4)	2 months	LOCM (Iodixanol, Iomeprol, Iobiditrol) IV	A3	M
Lee, 2011[69]	IV normal saline vs. IV NaHCO3	382	General	62-73	111 (29)	6 months	IOCM (Iodixanol) IA	A1	M
Manari, 2014[76]	IV Normal Saline vs High dose IV Normal Saline vs IV NaHCO3 vs High dose IV NaHCO3	592	Cardiovascular: STEMI meeting inclusion criteria	65	149 (25.2)	1 year	IOCM (Iodixanol) IA	A3	M
Masuda, 2007[80]	Normal saline vs. IV NaHCO3	59	Cr concentration >1.1mg/dl or estimated GFR <60 ml/min	75-76	23 (39)	2 days	LOCM (Iopamidol) IA	A3	M
Merten, 2004[82]	Normal saline + dextrose vs. IV NaHCO3 + dextrose	119	Stable renal insufficiency	66	16 (13)	2 days	LOCM (Iopamidol) Both IA and IV	A1	M
Motohiro, 2011[84]	IV normal saline vs. IV NaHCO3 + IV normal saline	155	GFR <60	71	47 (30)	1 month	LOCM (Iopamidol) IA	A3	M
Ozcan, 2007[87]	Normal saline vs. IV NaHCO3 + dextrose	264	General	40-87	67 (25)	2 days	LOCM (Ioxaglate) IA	A3	H

Evidence Table E-10. Summary of studies comparing IV sodium bicarbonate versus IV saline for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population included	Age, Range of means§	Sex, n female (%)‡	Mean followup	CM Route*	Definition of CIN*	Study limitations†
Ratcliffe, 2009 [93]	Normal saline + dextrose vs. IV NaHCO3 + dextrose	78	General	64-67	31 (39)	3 days	IOCM (Iodixanol) IA	A1	H
Tamura, 2009[124]	IV Normal Saline vs. IV Normal Saline+ NaHCO3	144	Cr level >1.1 to <2.0 mg/dl	72-73	18 (13)	7 days	LOCM (Iohexol) IA	A3	M
Thayssen, 2014[107]	IV Normal Saline vs IV Normal Saline + oral NAC vs IV Normal Saline + IV NaHCO3 vs IV Normal Saline + oral NAC + IV NaHCO3	715	STEMI	63	165 (23.1)	30 Days	IOCM (Iodixanol) IA	A1/A2	M
Ueda, 2011[111]	Normal saline vs. IV NaHCO3	59	Cr >1.1 mg/dl, eGFR <60ml/min	75-77	13 (22)	2 days	LOCM (Iohexol) IA	A3	H
Vasheghani, 2009[125]	IV normal saline vs. IV NaHCO3 + IV normal saline	265	General	62-63	45 (17)	5 days	IOCM (iodixanol), LOCM (Iohexol), HOCM (amidotrizoic acid) IA	A3	L
Vasheghani-Farahani, 2010[112]	0.45% saline vs. IV NaHCO3 + 0.45% saline	72	CHF	61	15 (20)	2 days	LOCM (Iohexol) IA	A3	L
Yeganehkhah, 2014[117]	IV Normal Saline vs. IV Normal Saline + IV NaHCO3	100	High risk of CIN	59.2	72 (48)	48hrs	LOCM (Iohexol) IA	A1	H

%=percent; CHF=congestive heart failure; CIN=contrast induced nephropathy; CM=contrast media; Cr=creatinine; GFR=glomerular filtration rate; HOCM=high osmolar contrast media; IA=intrarterial; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low osmolar contrast media; Mg/dl=milligram per deciliter; Ml/min=milliliter per minute; N=sample size; NaCl=sodium chloride; NaHCO3=sodium bicarbonate; NR=not reported; vs.=versus

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance; † Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias; ‡ Percent females in entire study population; § Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.; ;

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Briguori, 2007[22]	increase in serum creatinine >25% from baseline value after administration of contrast media		Saline plus NAC	2		111	11 (9.9)					
Briguori, 2007[22]	increase in serum creatinine >25% from baseline value after administration of contrast media		Bicarbonate plus NAC	3		108	2 (1.9)					
Briguori, 2007[22]	increase in serum creatinine >25% from baseline value after administration of contrast media		Saline plus ascorbic acid plus NAC	4		107	11 (10.3)					
Briguori, 2011[126]	Incidence of CIAKI		sodium bicarbonate + NAC	1	48 hours	146	30 (20.5)	0.47 (95% CI: 0.24 to 0.92)				
Briguori, 2011[126]	Incidence of CIAKI		RenalGuard: saline + NAC + RenalGuard System + furosemide	2		146	16 (11)					
Briguori, 2011[126]	Incidence of CIAKI	GFR<30 ml.min.1,73 m^2	sodium bicarbonate + NAC	1	48 hours	146	20 (29.5)	0.44 (95% CI: 0.19 to 0.98)				

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Briguori, 2011[126]	Incidence of CIAKI	GFR<30 ml.min.1,73 m^2	RenalGuard: saline + NAC + RenalGuard System + furosemide	2		146	11 (15)					
Briguori, 2011[126]	Increase >0.5 mg/dl		sodium bicarbonate + NAC	1	48 hours	146	22	p=<0.001				
Briguori, 2011[126]	Increase >0.5 mg/dl		RenalGuard: saline + NAC + RenalGuard System + furosemide	2		146	9					
Briguori, 2011[126]	Increase >25%		sodium bicarbonate + NAC	1	48 hours	146	19 (13)	p=<0.001				
Briguori, 2011[126]	Increase >25%		RenalGuard: saline + NAC + RenalGuard System + furosemide	2		146	4 (2.7)					
Briguori, 2011[126]	Increase >50%		sodium bicarbonate + NAC	1	48 hours	146	11 (7.5)	p=<0.001				
Briguori, 2011[126] (continued)	Increase >50%		RenalGuard: saline + NAC + RenalGuard System + furosemide	2		146	1 (0.7)					
Briguori, 2011[126],	Incidence of CIAKI	CIAKI risk score >11	Bicarbonate plus NAC	1	48 hours	146	11(14)	OR, 0.45 (95% CI: 0.15 to 1.36)				

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Briguori, 2011[126],	Incidence of CIAKI	CIAKI risk score >11	RenalGuard	2			146	5 (7)				
Cho, 2010[127]	Cr		Saline	1	72 hours	27	6	A1 v A2 p=0.78 A1 v A3 P=0.617 A1 v A4 P=0.342 A2 v A3 P=0.835 A2 v A4 P=0.525 A3 vA4 P=0.663				
Cho, 2010[127]	Cr		Bicarbonate plus saline	2		21	2					
Cho, 2010[127]	Cr		Oral fluids	3		22	1					
Cho, 2010[127]	Cr		Oral bicarbonates plus fluids	4		21	1					
Hafiz, 2012[128]	Incidence of CI-AKI		saline	2	48 hours	161	19 (11.8)	p=>0.05				
Hafiz, 2012[128]	Incidence of CI-AKI		bicarbonate	3		159	14 (8.8)					
Hafiz, 2012[128]	Incidence of CI-AKI	With NAC	saline	2	48 hours	81	8 (9.9)	P=>0				
Hafiz, 2012[128]	Incidence of CI-AKI	With NAC	bicarbonate	3		80	8 (10)					

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Hafiz, 2012[128]	Incidence of CI-AKI	Without NAC	saline	2	48 hours	80	11 (13.8)	p=>0.05				
Hafiz, 2012[128]	Incidence of CI-AKI	Without NAC	bicarbonate	3		79	6 (7.6)					
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Age (increasing years)	Saline	2	48 hours			OR, 1.05 (95% CI: 1.02 to 1.08), p=0.001				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Age (increasing years)	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Anemia	Saline	2	48 hours			OR, 1.97 (95% CI: 0.42 to 9.29), p=0.390				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Anemia	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Contrast volume >3ml/kg	Saline	2	48 hours			OR, 1.10 (95% CI: 1.00 to 1.20), p=0.038				
Hafiz, 2012[128] (continued)	Risk factors associated with higher incidence of CI-AKI	Contrast volume >3ml/kg	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Diabetes	Saline	2	48 hours			OR, 1.57 (95% CI: 0.69 to 3.55), p=0.281				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Diabetes	Bicarbonate	3								

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Diuretics	Saline	2	48 hours			OR, 3.4 (95% CI: 1.46 to 7.98), p=0.005				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Diuretics	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	female	Saline	2	48 hours			OR, 0.49 (95% CI: 0.21 to 1.13), p=0.095				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	female	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	GFR	Saline	2	48 hours			OR, 0.99 (95% CI: 0.98 to 1.01), p=0.435				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	GFR	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Higher baseline creatinine level	Saline	2	48 hours			OR, 0.64 (95% CI: 0.35 to 1.19), p=0.161				
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Higher baseline creatinine level	Bicarbonate	3								
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Use of ACE inhibi	Saline	2	48 hours			OR, 1.12 (95% CI: 0.51 to 2.50), p=0.775				

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Hafiz, 2012[128]	Risk factors associated with higher incidence of CI-AKI	Use of ACE inhibi	Bicarbonate	3								
Klima, 2012[129]	Incidence of CIN	Creatinine increase >25%	saline	1	48	89	1 (1)	p=0.02				
Klima, 2012[129]	Incidence of CIN	Creatinine increase >25%	long term sodium bicarbonate	2		87	8 (9)					
Klima, 2012[129]	Incidence of CIN	Creatinine increase >25%	short term sodium bicarbonate	3		82	8 (10)					
Klima, 2012[129]	Incidence of CIN	Creatinine increase >44umol/l	saline	1	48 hours	89	1 (1)	p=0.03				
Klima, 2012[129]	Incidence of CIN	Creatinine increase >44umol/l	long term sodium bicarbonate	2		87	7 (8)					
Klima, 2012[129]	Incidence of CIN	Creatinine increase >44umol/l	short term sodium bicarbonate	3		82	6 (7)					
Maioli, 2008[130]	Absolute increase of at least 0.5mg/dl over baseline serum creatinine within 5 days after administration		Saline plus NAC	2	5 days	252	29 (11.5)	p=0.60				
Maioli, 2008[130]	Absolute increase of at least 0.5mg/dl over baseline serum creatinine within 5 days after administration		Bicarbonate plus oral NAC	3		250	25 (10)					

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Maioli, 2011[131] (continued)	Incidence of CI-AKI	>75 years	Late hydration	2		36	15 (41.7)					
Maioli, 2011[131]	Incidence of CI-AKI	>75 years	Early hydration	3		38	8 (21.1)					
Maioli, 2011[131]	Incidence of CI-AKI	anterior myocardial infarction	No hydration	1	3 days	65	22 (33.8)	All arms p=0.07				
Maioli, 2011[131]	Incidence of CI-AKI	anterior myocardial infarction	Late hydration	2		63	16 (25.4)					
Maioli, 2011[131]	Incidence of CI-AKI	anterior myocardial infarction	Early hydration	3		61	12 (19.7)					
Maioli, 2011[131]	Incidence of CI-AKI	Diabetes mellitus	No hydration	1	3 days	34	10 (29.4)	p=0.24 all arms				
Maioli, 2011[131]	Incidence of CI-AKI	Diabetes mellitus	Late hydration	2		31	11 (35.5)					
Maioli, 2011[131]	Incidence of CI-AKI	Diabetes mellitus	Early hydration	3		31	5 (16.1)					
Maioli, 2011[131]	Incidence of CI-AKI	eGFR <60ml/min	No hydration	1	3 days	34	10 (29.4)	All arms p=0.14				
Maioli, 2011[131]	Incidence of CI-AKI	eGFR <60ml/min	Late hydration	2		46	12 (26.1)					
Maioli, 2011[131]	Incidence of CI-AKI	eGFR <60ml/min	Early hydration	3		40	6 (15.0)					
Maioli, 2011[131]	Incidence of CI-AKI	High CIN risk	No hydration	1	3 days	52	18 (34.6)	All arms p=0.28				
Maioli, 2011[131]	Incidence of CI-AKI	High CIN risk	Late hydration	2		46	14 (26.1)					
Maioli, 2011[131] (continued)	Incidence of CI-AKI	High CIN risk	Early hydration	3		45	11 (24.4)					
Maioli, 2011[131]	Incidence of CI-AKI	Left ventricular ejection fraction <40%	No hydration	1	3 days	61	24 (39.3)	All arms p=0.04				

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Maioli, 2011[131]	Incidence of CI-AKI	Left ventricular ejection fraction <40%	Late hydration	2		58	20 (34.5)					
Maioli, 2011[131]	Incidence of CI-AKI	Left ventricular ejection fraction <40%	Early hydration	3		56	12 (21.4)					
Maioli, 2011[131]	Incidence of CI-AKI	Volume of contrast media to eGFR ratio >3.7%	No hydration	1	3 days	50	15 (30.0)	All arms p=0.20				
Maioli, 2011[131]	Incidence of CI-AKI	Volume of contrast media to eGFR ratio >3.7%	Late hydration	2		55	15 (27.3)					
Maioli, 2011[131] (continued)	Incidence of CI-AKI	Volume of contrast media to eGFR ratio >3.7%	Early hydration	3		48	9 (18.8)					
Maioli, 2011[131]	Incidence of CI-AKI, whole population		No hydration	1	3 days	150	41 (27.3)	p=0.001 all arms				
Maioli, 2011[131]	Incidence of CI-AKI, whole population		Late hydration	2		150	34 (22.7)					
Maioli, 2011[131]	Incidence of CI-AKI, whole population		Early hydration	3		150	18 (12.0)					
Pakfetrat, 2009[132]	Development of CIN associated kidney injury using rifles criteria		Saline	1	48 hours	96	16 (16.6)	All arms p=0.4				
Pakfetrat, 2009[132]	Development of CIN associated kidney injury using rifles criteria		Bicarbonate plus saline	2		96	4 (4.2)					
Pakfetrat, 2009[132]	Development of CIN associated kidney injury using rifles criteria		Saline plus acetazolamide	3		94	5 (5.3)					

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Schmidt, 2007[133]	impairment of renal function occurring within 72 hours of administering contrast media, indicated by an absolute increase in the serum creatinine level of 0.5 mg/dL or more.		NAC plus bicarbonate	2	72 hours	47	7 (14.9)	p=0.71				
Schmidt, 2007[133]	impairment of renal function occurring within 72 hours of administering contrast media, indicated by an absolute increase in the serum creatinine level of 0.5 mg/dL or more.		NAC plus saline	3		49	6 (12.2)					
Tamura, 2009[124]	increase >25% or >0.5 mg/dl in serum Cr within the first 3 days after the procedure compared to baseline value		Normal Saline	1	3 days	72	9 (12.5)	p=0.17				

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Tamura, 2009[124]	increase >25% or >0.5 mg/dl in serum Cr within the first 3 days after the procedure compared to baseline value		Normal Saline + Bicarbonate	2		72	1 (1.4)					
Vasheghani -Farahani, 2009[125]	absolute (0.5 mg/dL) or relative (25%) increase over baseline creatinine level 48 hours after expo-sure to a contrast agent.		saline	1	2 days	130	7 (5.9)	OR NR (95% CI: 0.45 to 3.5) p=0.6	5 days	130	8 (6.6)	OR NR (95% CI: 0.4-4.2) p=0.60
Vasheghani -Farahani, 2009[125]	absolute (0.5 mg/dL) or relative (25%) increase over baseline creatinine level 48 hours after expo-sure to a contrast agent.		Saline+bicarbo nate	2		135	9 (7.4)			135	11 (8.5)	
Vasheghani -Farahani, 2009[125]	at least a 25% decrease in baseline eGFR 48 hours after contrast exposure		saline	1	2 days	130	3 (2.6)	OR 1.26(95% CI: 0.6 to 9.3) p=0.3	5 days	130	5 (4.2)	OR1.30(95% CI: 0.4 to 4.2) p=0.60
Vasheghani -Farahani, 2009[125]	at least a 25% decrease in baseline eGFR 48 hours after contrast exposure		Bicarbonate plus saline	2		135	7 (5.9)			135	7 (5.5)	

Evidence Table E-11. Contrast-induced nephropathy outcomes in studies comparing of IV sodium bicarbonate and IV saline placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Yeganehkhah, 2014[117]	Incidence of CIN	IV NS	1	48 hrs	50	7	P=0.944					
Yeganehkhah, 2014[117]	Incidence of CIN	NaHCO3 + IV NS	2		50	20						

%=percent; A1=arm 1; A2=arm 2; A3=arm 3; A4=arm 4; ACE inhibi= angiotensin converting enzyme inhibitor; CI=confidence interval; CIAKI=contrast induced acute kidney injury; CIN=contrast induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; H=hour; HD=hemodialysis; Kg=kilogram; LVEF=left ventricular ejection fraction; Mg/dl=milligram per deciliter; ml/min/1.73m^2=milliliter per minute per 1.73m squared; ml=milliliter; Mmol/l=millimole per liter; N=sample size; NAC=N-acetylcysteine; NS=non-significant; OR=odds ratio; P=p-value; RR=relative risk; SCr=serum creatinine ; SG=subgroup; Umol/l=micromole per liter;

Evidence Table E-12. Changes in serum creatinine outcomes in studies comparing of IV sodium bicarbonate and IV saline

Author year	Measure	SG	Intervention	Arm	Base-line N anal-yzed	Mean base-line value (SD)	Time point 1	Time point 1 N anal-yzed	Mean (SD)	Comparison* statistics at time point 1	Time point 2	Time point 2 N anal-yzed	Mean (SD)	Comparison* statistics at time point 2
Adolph, 2008[134]	Short term		Saline plus dextrose	1	74	Mean (.35) (Max: 2.60 Min: 1.20)	2 days	74	Mean (.40) (Max: 3.14 Min: 1.05)	p=NS				
Adolph, 2008[134]	Short term		Bicarbonate plus dextrose	2	71	Mean (0.51) (Max: 4.60 Min: 1.20)		71	Mean (.52) (Max: 4.86 Min: 0.99)					
Kooiman, 2014[65]	Mean increase in SCr from baseline, %		Normal saline	1			48-96 hours	273	1.5(14.2)	Mean difference: -0.3% (95% CI: -2.7-2.1) P<0.0001				
Kooiman, 2014[65]	Mean increase in SCr from baseline, %		IV Sodium Bicarbonate + normal saline	2				263	1.2(13.3					
Yeganehkhah, 2014[117]	Serum Creatinine levels		IV NS	1	50	1.08 (0.32)	48	50	1.13 (0.28)	0.039				
Yeganehkhah, 2014[117]	Serum Creatinine levels		NaHCO3 + IV NS	2	50	1.17 (0.32)		50	1.19 (0.33)	0.624				

%=percent; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; H=hour; IQR=interquartile range; LVEF=left ventricular ejection fraction; Max=maximum; Mg/dl=milligram per deciliter; Min=minimum; Ml/min=milliliter perminute; N=sample size; NAC=N-acetylcysteine; NaCl=sodium chloride; NR=not reported; NS=non-significant; P=p-value; SD=standard deviation; SG=subgroups; SrCr=serum creatinine; Umol/l=micromole per liter; V=versus;

Evidence Table E-13. Summary of other outcomes reported in studies comparing IV sodium bicarbonate and IV saline for the prevention of contrast-induced nephropathy

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Beyazal, 2014[15]	NR	NR	NR	NR	NR
Boucek, 2013[19]	Arm 1: 5.85 % Normal saline Arm 2: NaHCO3	At 1 month Arm1: 0/59 (0) Arm2: 0/61 (0) P=NR	Post-procedure within 1 month Arm1: 0/59 (0) Arm2: 0/61 (0) P=NR After 1 month Arm1: 2/59 (3.39) Arm2: 1/61 (1.64) P=NR	Duration of hospitalization Arm1: 8.4 (12.9) Arm2: 8.0 (10.0) P=NR	NR
Brar, 2008[20]	Arm1: IV normal saline Arm 2: NaHCO3	At 6 months Arm1: 7/165 (3.9) Arm2: 4/158 (2.3) P=0.54	At 1 month Arm1: 2/165(2) Arm2: 1/158 (1) P=NR At 6 months Arm1: 4/165 (2) Arm2: 2/158 (1) P=NR	NR	NR
Castini, 2010[28]	Arm1: IV normal saline Arm 2: NaHCO3 + dextrose	NR	NR	NR	NR
Gomes, 2012[40]	Arm1: IV normal saline Arm 2: NaHCO3 + dextrose	In-hospital mortality, short-term at 48 hours Arm1: 5/151 (3.4) Arm2: 7/150 (4.7) P=0.81	At 48 hours Arm1: 0/151 (0) Arm2: 0/150 (0) P=NR	Arm1: 8.6 (9.7) Arm2: 7.5 (10) P=0.35	NR
Kama, 2014[54]	Arm1: IV Normal Saline Arm2: IV NAC in Normal Saline Arm3: IV NaHCO3 in Normal Saline	NR	Need for RRT 1 month Arm1: 0 (0) Arm2: 3 (803) Arm3: 2 (5.6) p=NR	NR	NR
Koc, 2013[64]	Arm1: IV normal saline Arm 2: NaHCO3	NR	NR	NR	NR
Kooiman, 2014[65]	Arm1: IV Normal Saline Arm2: IV NaHCO3 + IV Normal Saline	NR	NR	NR	Acute Heart Failure at 48-96 hours Arm1: 6/281 (2.1) Arm2: 0/267 (0) p=0.03

Evidence Table E-13. Summary of other outcomes reported in studies comparing IV sodium bicarbonate and IV saline for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Lee, 2011[69]	Arm1: IV normal saline Arm 2: NaHCO3	All-cause at 1 month Arm1: 0/189 (0) Arm2: 1/193 (0.5) P=1.0 At 1-6 months Arm1: 2/189 (1.1) Arm2: 5/193 (2.6) P=0.45 Cumulative at 6 months Arm1: 2/189 (1.1) Arm2: 6/193 (3.1) P=0.45	At 1 month Arm1: 1/189 (0.5) Arm2: 1/193 (0.5) P=1.0 At 1-6 month Arm1: 0/189(0) Arm2: 3/193 (1.6) P=0.25 At 6 months Arm1: 1/189 (0.5) Arm2: 4/193 (2.1) P=0.37	NR	Myocardial infarction at 1 month Arm1: 0/189 (0) Arm2: 0/1193 (0) P=NR At 1-6 month Arm1: 0/189 (0) Arm2: 0/1193 (0) P=NR At 6 months Arm1: 0/189 (0) Arm2: 0/193 (0) P=NR
Manari, 2014[76]	Arm1: IV Normal Saline Arm2: High dose IV Normal Saline Arm3: IV NaHCO3 Arm4: High dose IV NaHCO3	NR	Timepoint: NR Arm1: 0/151 (0) Arm2: 0/142 (0) Arm3: 0/145 (0) Arm4: 0/154 (0) p=NR	NR	NR
Masuda, 2007[80]	Arm 1: Normal saline Arm 2: IV NaHCO3	At 48 hours Arm1: 2/29 (7) Arm2: 0/30 (0) P=0.24	Time point: NR Arm1: 3/29 (10) Arm2: 1/30 (3) P=0.35	NR	NR
Merten, 2004[82]	Arm 1: Normal saline + dextrose Arm 2: IV NaHCO3 + dextrose	NR	NR	NR	NR
Motohiro, 2011[84]	Arm 1: IV normal saline Arm 2: IV NaHCO3 + IV normal saline	NR	Time point: NR Arm1: 0/77 (0) Arm2: 0/78 (0) P=NR	NR	NR
Ozcan, 2007[87]	Arm 1: Normal saline Arm 2: Normal saline + NAC Arm 2: IV NaHCO3 + dextrose	NR	At 48 hours Arm1: 1/88 (1) Arm2: 0/88 (0) Arm3: 1/88 (1) P=NR	NR	Congestive heart failure at 48 hours Arm1: 0/88 Arm2: 0/88 Arm3: 0/88 P=NR
Ratcliffe, 2009 [93]	Arm 1: Normal saline + dextrose Arm 2: IV NaHCO3 + dextrose	NR	NR	NR	NR

Evidence Table E-13. Summary of other outcomes reported in studies comparing IV sodium bicarbonate and IV saline for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Tamura, 2009[124]	Arm1: IV Normal Saline Arm2: IV Normal Saline+ NaCHO3	NR	Need for Dialysis At 7 days Arm1:1/72 (1.3) Arm2:0/72 (0) p=0.99	NR	NR
Thayssen, 2014[107]	Arm1: IV Normal Saline Arm2: IV Normal Saline + oral NAC Arm3: IV Normal Saline + IV NaHCO3 Arm4: IV Normal Saline + oral NAC + IV NaHCO3	NR	30 Days Arm1: 0/181 (0) Arm2: 0/176 (0) Arm3: 0/181 (0) Arm3: 0/177 (0) p=NR	NR	Cardiac major events, composite (cardiac death, myocardial infarction, target vessel revascularization) Arm1: 4/181 (2.2) Arm2: 0/176 (0) Arm3: 6/181 (3.6) Arm3: 3/177 (1.7) p=0.13
Ueda, 2011[111]	Arm 1: Normal saline Arm 2: IV NaHCO3	Time point: NR Arm1: 3/29(10) Arm2: 2/30 P=NR	NR	Time point: NR Arm1: 22.8 (17.9) Arm2: 21.4 (19.6) P=0.78	NR
Vasheghani, 2009[125]	Arm 1: IV normal saline Arm 2: IV NaHCO3 + IV normal saline	NR	NR	NR	NR
Vasheghani-Farahani, 2010[112]	Arm 1: 0.45% saline Arm 2: IV NaHCO3 + 0.45% saline	NR	NR	NR	NR
Yeganehkhah, 2014[117]	Arm 1: IV NS Arm 2: IV NaHCO3 + IV NS	NR	NR	NR	NR

%=percent; N=sample; NaCl=sodium chloride; NaHCO3=sodium bicarbonate; NR=not reported; NS=normal saline; P=p-value; RRT=renal replacement therapy; SD=standard deviation;

Evidence Table E-14. Adverse events in studies comparing IV sodium bicarbonate versus IV saline

Author, Year	Adverse events
Boucek, 2013[19]	Other: local bleeding at the site of arterial puncture, Local bleeding at the site of arterial puncture necessitating transfusion and/or surgical intervention. No significant difference in occurrence between the two groups.
Brar, 2008[20]	Myocardial infarction: 2 cases within 6 months in sodium bicarbonate group and 4 cases in sodium chloride group CVA: 1 case within 6 months in sodium bicarbonate group and 7 cases in sodium chloride group
Castini, 2010[28]	only reported acute renal failure (necessitating HD, ultrafiltration or peritoneal dialysis never occurred.
Cho, 2010[127]	Other: in-house mortality 0 in all arms
Kama, 2014[54]	No contrast or treatment induced adverse events were detected during emergency department care
Kooiman, 2014[65]	Need additional imaging: 1 patient in saline arm; Fluid overload: 1 pt req stopping saline- 4 pts req furosemide - 1 pt required hospitalization
Manari, 2014[76]	Death at 12 months: 25 total; 16 occurred within 30 days
Masuda, 2007[80]	Heart failure: 22 cases of heart failure within 2 days of admission, 11 in each group Anaphalaxis acute renal failure requiring hemodialysis: 4 cases in total 1 in sodium bicarbonate group and 3 in sodium chloride group Circulatory failure with lactic acidosis: 10 cases in total 4 in sodium bicarbonate group and 6 in sodium chloride group Respiratory failure requiring mechanical ventilation: 8 cases in total 3 in sodium bicarbonate group and 5 in sodium chloride group
Ozcan, 2007[87]	No AES related to tx
Ratcliffe, 2009[93]	Other: Serious adverse events, No serious adverse events from any of the medications given or from the procedure itself
Tamura, 2009[124]	NR
Thayssen, 2014[107]	Within 3 days: 3 (0.3%) patients had a target lesion revascularization, 4 (0.6%) had a target vessel revascularization. 11 (1.5%) had a new angiogram for a clinical reason without intervention 9 (1.3%)patients had a nonculprit artery PCI. Within 30 days: 7 (1.0%) patients had a target lesion revascularization, 11 (1.5%) had a target vessel revascularization. 20 (2.8%) had a new angiogram for a clinical reason without intervention, 24 (3.3%) patients had a nonculprit artery PCI.
Ueda, 2011[111]	Heart failure: 5 patients in NaBicarbonate6 Patients in Na Chloride Anaphalaxis
Yeganehkhah, 2014[117]	NR

AE=adverse events; CVA=cardiovascular accident; HD=hemodialysis; Na=sodium; NR=not reported

Evidence Table E-15. Summary of studies comparing N-acetylcysteine plus IV normal saline versus IV sodium bicarbonate for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N randomized (N analyzed)	Population	Age (years) or range of means §	Number. female (%)‡	Total followup	CM route	Primary definition of CIN*	Study limitations†
Castini, 2010[28]	IV normal saline Oral NAC +IV normal saline IV NaHCO3 in 5% dextrose in water without NAC	156 (156)	Baseline SrCr 1.2 to 4 mg/dl.	70-73	19 (12)	5 days (labs were drawn at 24 hours, 48 hours, and at 5 days after the procedure)	IOCM (Iodixanol) IA	A1 (secondary endpoint: A2)	M
Heguilen, 2013[45]	IV NaHCO3 in 5% dextrose in water NAC + normal saline in 5% dextrose in water without NAC	133 (123)	Stable SrCr 1.25 mg/dl (110 micromol/l) to 4.5 mg/dl (364.5 micromol/l), or Cockcroft-Gault-estimated creatinine clearance < 45 ml/min	65-69	34 (28)	2-3 days	LOCM (Ioversol) IA	A1	M
Kama, 2014[54]	IV Normal Saline vs IV NAC in Normal Saline vs IV NaHCO3 in Normal Saline	107 (107)	High risk of CIN, using Mehran score (>5 points)	71	48 (45)	1 month	LOCM (Iohexol) Route NR	A3	M
Ozcan, 2007[87]	Oral NAC + IV normal saline IV NaHCO3 in 5% dextrose in water without NAC	264 (NR)	Baseline SrCr >1.2 to 4 mg/dl	67-70	67 (25)	48 hours	LOCM (Ioxaglate) IA	A3	H
Ratcliffe, 2009 [93]	IV and oral NAC + IV normal saline in 5% dextrose IV NaHCO3 in 5% dextrose without NAC	118 (78)	Renal insufficiency and/or diabetes mellitus (renal insufficiency defined asSrCr > 132.6 µmol/L (1.5 mg/dl) in men, and > 114.9 µmol/L(1.3 mg/dl) in women) or reduced calculated creatinine clearance (< 1.002 mL/s) using Cockcroft-Gault formula)	66	31 (40)	7 days (labs were drawn at 24, 72, and 168 hours after the procedure)	IOCM (Iodixanol) IA	A1*	H

Evidence Table E-15. Summary of studies comparing N-acetylcysteine plus IV normal saline versus IV sodium bicarbonate for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	N randomized (N analyzed)	Population	Age (years) or range of means §	Number. female (%)‡	Total followup	CM route	Primary definition of CIN*	Study limitations†
Shavit, 2009[101] (prospective, partially blinded trial)	IV NaHCO3 in 5% dextrose in water oral NAC + intravenous normal saline	93 (87)	CKD stage III–IV (estimated glomerular filtration rate 15-60 mL/min calculated by the MDRD formula)	71-72	19 (22)	48 hours	LOCM (Iopamidol) IA	A1 (authors also used a definition of SrCr increase of ≥ 0.3 mg/dL)	H
Thayssen, 2014[107]	IV Normal Saline vs IV Normal Saline + oral NAC vs IV Normal Saline + IV NaHCO3 vs IV Normal Saline + oral NAC + IV NaHCO3	715	STEMI	63	165 (23.1)	30 Days	IOCM (Iodixanol) IA	A3	M
Yeganehkhah, 2014[117]	IV Normal Saline + IV NaHCO3 vs Oral NAC + IV Normal Saline	100	High risk of CIN	59.2	72 (48)	48hrs	LOCM (Iohexol) IA	A1	H

%=percent; CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; IA=intrarterial; IOCM=iso-osmolar contrast media; IV-intravenous; LOCM=low-osmolar contrast media; MDRD= Modification of Diet in Renal Diseases; Mg/dl=milligram per deciliter; Micromole/l=micromole per liter; Ml/min=milliliter per minute; Ml/s=milliliter per second; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; NR=not reported; SrCr=serum creatinine; STEMI= ST Elevation Myocardial Infarction; Umol/l=micromole/liter

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1);> 25% (A1*); ≥0.5 mg/dl (A2); ->25% or 0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms if the mean age for the whole population is not reported.

*n/N refers to number of events divided by number at risk.

Evidence Table E-16. Contrast-induced nephropathy outcomes in the study comparing N-acetylcysteine plus IV saline versus IV sodium bicarbonate that was not included in the meta-analysis

Author, year	CIN definition	Intervention	Arm	Time point 1	Time point 1 N analyzed	N (%) with outcome at time point 1	Comparison statistics at time point 1
Shavit, 2009[101]	Increase in SrCr ≥ 25% from baseline	IV $NaHCO_3$ in 5% dextrose in water	1	48 hours	51	5 (9.8)	p=NS
Shavit, 2009[101]	Increase in SrCr ≥ 25% from baseline	Oral NAC + intravenous normal saline	2		36	3 (8.3)	
Shavit, 2009[101]	Increase in plasma creatinine of ≥ 0.3 mg/dL or more from baseline	IV $NaHCO_3$ in 5% dextrose in water	1	48 hours	51	8 (15.7)	p=NS
Shavit, 2009[101]	Increase in plasma creatinine of ≥ 0.3 mg/dL or more from baseline	Oral NAC + intravenous normal saline	2		36	6 (16.7)	
Yeganehkhah, 2014[117]	Incidence of CIN	$NaHCO_3$ + IV NS	1		50	20	P=0.944
Yeganehkhah, 2014[117]	Incidence of CIN	Oral NAC + IV NS	2		50	6	

%=percent; A1=arm 1; A2=arm 2; A3=arm 3; CI=confidence interval; CIN=contrast-induced nephropathy; SrCr=creatinine; GFR=glomerular filtration rate; H=hour; Mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NaCl=sodium chloride; $NaHCO_3$=sodium bicarbonate; NS=non-significant; RR=risk ratio; SrCr=serum creatinine

Evidence Table E-17. Summary of other outcomes reported in studies comparing N-acetylcysteine plus IV saline versus IV sodium bicarbonate for the prevention of contrast-induced nephropathy

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Castini, 2010[28]	Arm1: IV normal saline Arm2: Oral NAC + IV normal saline Arm3: IV NaHCO3 in 5% dextrose in water	0/156 (0)	-0/156 (0)	NR	NR
Heguilen, 2013[45]	Arm 2: IV NaHCO3 in 5% dextrose in water Arm 3: NAC + IV NaHCO3 in 5% dextrose in water Arm 4: NAC + IV normal saline in 5% dextrose in water	NR	NR	NR	Heart failure at 48 hours: Arm 1: 0/80 (0) Arm 2: 0/43 (0) Arm 3: 0/38 (0)
Kama, 2014[54]	Arm1: IV Normal Saline Arm2: IV NAC in Normal Saline Arm3: IV NaHCO3 in Normal Saline	NR	Need for RRT 1 month Arm1: 0 (0) Arm2: 3 (803) Arm3: 2 (5.6) p=NR	NR	NR
Ozcan, 2007[87]	Arm1: IV normal saline Arm2: Oral NAC + IV normal saline Arm3: IV NaHCO3 in 5% dextrose in water	NR	At 48 hours Arm1: 1/88 (1) Arm2: 0/88 (0) Arm3: 1/88 (1); p=NR	NR	Congestive heart failure at 48 hours 0/264 (0)
Ratcliffe, 2009 [93]	Arm1: IV normal saline in 5%dextrose in water Arm2: IV and oral NAC + IV normal saline in 5% dextrose in water Arm3: IV NaHCO3 in 5% dextrose in water Arm4: IV and oral NAC + IV NaHCO3 in 5% dextrose in water	NR	NR	NR	NR
Shavit, 2009 [101]	Arm1: IV NaHCO3 in 5% dextrose in water Arm2: Oral NAC + intravenous normal saline	NR	0/87 (0)	NR	NR
Thayssen, 2014[107]	Arm1: IV Normal Saline Arm2: IV Normal Saline + oral NAC Arm3: IV Normal Saline + IV NaHCO3 Arm4: IV Normal Saline + oral NAC + IV NaHCO3	NR	30 Days Arm1: 0/181 (0) Arm2: 0/176 (0) Arm3: 0/181 (0) Arm3: 0/177 (0) p=NR	NR	Cardiac major events, composite (cardiac death, myocardial infarction, target vessel revascularization) Arm1: 4/181 (2.2) Arm2: 0/176 (0) Arm3: 6/181 (3.6) Arm3: 3/177 (1.7) p=0.13

Yeganehkhah, 2014[117]	Arm1: IV NaHCO3 + IV NS Arm 2: Oral NAC + IV NS	NR	NR	NR	NR

Evidence Table E-17. Summary of other outcomes reported in studies comparing N-acetylcysteine plus IV saline versus IV sodium bicarbonate for the prevention of contrast-induced nephropathy (continued)

%=percent; CIN=contrast-induced nephropathy; CKD=chronic kidney disease; CM=contrast media; H=high risk; IA=intrarterial; IV=intravenous; M=moderate risk; Mg/dl=milligram per deciliter; MDRD=Modification of Diet in Renal Disease; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; SrCr=serum creatinine;

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1);> 25% (A1*); ≥0.5 mg/dl (A2); ->25% or 0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms if the mean age for the whole population is not reported.

*n/N refers to number of events divided by number at risk.

Evidence Table E-18. Reported adverse events in studies comparing N-acetylcysteine plus IV saline versus IV sodium bicarbonate

Author, Year	Adverse events
Castini, 2010[28]	Acute renal failure necessitating HD, ultrafiltration or peritoneal dialysis did not occur.
Heguilen,2013[45]	Volume administration resulted in a moderate although not significantly different increase among the three groups in both systolic and diastolic blood pressure, but none of the patients who completed the study developed heart failure or respiratory distress (ten patients did not complete the study; seven of those were lost to follow-up).
Kama, 2014[54]	No contrast or treatment induced adverse events were detected during emergency department care
Ozcan, 2007[87]	No adverse events were reported to have occurred related to active treatments.
Ratcliffe, 2009[93]	There were no reported serious adverse events from any of the medications given or from the procedure itself.
Shavit, 2009[101]	No patient developed more than a 50% rise in serum creatinine or required renal replacement therapy during the hospitalization.
Thayssen, 2014[107]	Within 3 days: 3 (0.3%) patients had a target lesion revascularization, 4 (0.6%) had a target vessel revascularization. 11 (1.5%) had a new angiogram for a clinical reason without intervention 9 (1.3%)patients had a nonculprit artery PCI. Within 30 days: 7 (1.0%) patients had a target lesion revascularization, 11 (1.5%) had a target vessel revascularization. 20 (2.8%) had a new angiogram for a clinical reason without intervention, 24 (3.3%) patients had a nonculprit artery PCI.
Yeganehkhah, 2014[117]	NR

HD=hemodialysis; PCI=percutaneous coronary intervention

Evidence Table E-19. Summary of studies comparing statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population included	No. female (%)[‡]	Age, range of means[§]	Mean followup	CM Route*	Definition of CIN*	Study limitations†
Abaci, 2015[1]	IV normal saline v risovustatin + IV normal saline	208	CKD	66((32)	67	48-72 hours	LOCM (Ioversol) IA	A2	M
Acikel, 2010[2]	IV Normal Saline vs. IV Normal Saline + Oral Atorvastatin vs. IV Normal Saline + Chronic Statin Therapy (non-randomized group)	240	LDL cholesterol >70 mg/dl	88 (37)	60	48 hours	LOCM (Iohexol) IA	NR	M
Han, 2013[43]	Low-dose Oral Atorvastatin + Oral Probucol vs. High-dose Oral Atorvastatin + Oral Probucol vs. High-dose Oral Atorvastatin	107	Coronary heart disease	90 (41)	NR	48 hours	LOCM (Iopamidol) NR	NR	H
Han, 2014[44]	IV normal saline vs. rosuvastatin +IV NS (hydration at discretion of clinicians)	2998	T2DM and stage 2-3 CKD	1044 (34)	61	72 hours CIN 30 days other	IOCM (Iodixanol) IA	A3	H
Jo, 2008[51]	Placebo + IV 0.45% saline vs. Simvastatin + IV 0.45% saline	247	≥Stage 3 CKD (CrCl≤ 60 ml/min or SrCr ≥1.1 mg/dl)	68 (38)	65-66	48 hr (Sr Cr/CIN) 1 and 6 months, other outcomes	IOCM (Iodixanol) IA	A3	M
Jo, 2014[53]	Regular Atorvastatin dose vs High Atorvastatin dose	218	STEMI	33 (15.1)	58-61	6 months	NR IA	A3	M
Kaya, 2013[56]	Oral Atorvastatin + IV Normal Saline vs. Oral Rosuvastatin + IV Normal Saline	192	STEMI and creatinine clearance >60ml//min	49 (25.5)	62-64	48 hours	LOCM (Iopromide) IA	A3	H
Leoncini, 2014[71]	No Rosuvastatin vs. Rosuvastatin	504	ACS	173 (34)	66	6 months	IOCM (Iodixanol) IA	A3	M
Li, 2012 [72]	Placebo (undefined) + IV normal saline vs. atorvastatin + IV normal saline	161	ACS: acute STEMI	39 (24)	65-66	72 hr (CIN) 1 month (other outcomes)	LOCM (Iopromide) IA	A3	M
Li, 2014[73]	Coronary heart disease	208	Coronary heart disease	85 (41)	60-62	24 hours	LOCM (Iopamidol) IA	A3	H
Liu, 2014[74]	Risovustatin vs Atorvastatin	1078	CKD	244 (22.6)	57-65	72 hours	LOCM IA	A2	H
Ozhan, 2010[88]	NAC + IV normal salinevs. NAC + Atorvastatin +IV normal saline	130	General	53 (40)	54-55	48 hours	LOCM (Iopamidol) IA	A3	M

Evidence Table E-19. Summary of studies comparing statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population included	No. female (%)‡	Age, range of means§	Mean followup	CM Route*	Definition of CIN*	Study limitations†
Patti, 2011[89]	Placebo vs. Atorvastatin (All patients received aspirin (100 mg/day) and clopidogrel 600-mg load >3 hours before the procedure)	241	ACS: unstable angina, or non-STEMI (statin naïve)	54 (22)	65-66	48 hours	LOCM (Iobitridol) IA	A3	L
Qiao, 2015[91]	IV saline vs Rosuvatatin + IV saline	120	T2DM, mild to moderate CKD	NR	NR	72 hours	IA	A2	H
Quintavalle, 2012[92]	NAC + IV $NaHCO_3$ vs. atorvastatin + NAC + IV $NaHCO_3$	410	≥Stage 3 CKD	187 (45)	70	48 hrs (CIN) 1 year (other outcomes)	IOCM (Iodixanol) IA	A1	M
Sanei, 2014[98]			General	74 (31.3)	58	72 hours	LOCM IA	NS	L
Shehata, 2015[102]	IV saline + oral NAC vs Atorvastatin + IV saline + oral NAC	130	chronic stable angina; mild or moderate CKD	63 (48.4)	55-57	72 hours	IA	A2	L
Toso, 2010[109]	Placebo + IV normal saline + NAC vs. atorvastatin + IV normal saline + NAC	304	≥Stage 3 CKD	108 (35)	75-76	Within 5 days (CIN) 1 month (other outcomes)	IOCM (Iodixanol) IA	A2	M
Xinwei, 2009[116]	Simvastatin 20mg + IV normal saline vs.simvastatin 80mg + IV normal saline	228	ACS: unstable angina, STEMI, or non-STEMI	146 (64)	65-66	48 hours	IOCM (Iodixanol) IA (patients with CKD) LOCM (Iohexol) IA (other patients)	A3	M
Yun, 2014[118]	IV normal saline vs. Risovustatin + IV saline	824	General population receiving PCI	284 (34.4)	63-64	72 hours	LOCM (Ioversol) or IOCM (Iohexol) Not stratified. IA	A2	H
Zhang, 2015[119]	Placebo vs Rosuvastatin	712 moderat e dose 220 high dose	T2DM, CKD stage 2 or 3	205 (28.7) low dose 57 (25.9) high dose	61	72 hours	IA	A2	M

Evidence Table E-19. Summary of studies comparing statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy and other outcomes (continued)

%=percent; ACS=acute coronary syndrome; CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; IA=intrarterial; IOCM=iso-osmolar contrast media; LOCM=low osmolar contrast media; Mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; NR=not reported; NS=normal saline; STEMI=ST Elevation Myocardial Infarction; T2DM=type 2 diabetes mellitus; vs.=versus

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table E-20. Contrast induced nephropathy outcomes in studies comparing statin plus IV saline versus IV saline with or without placebo that are not included in the meta-analysis

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Abaci, 2015[1]	Incidence of CIN		IV normal saline	1	48-72 hours	105	9 (8.5)	P=0.44				
Abaci, 2015[1]	Incidence of CIN		Risovustain + IV normal saline	2	48-72 hours	103	6 (5.8)					
Kaya, 2013[56]	SCr ≥0.5 mg/dl or ≥25% from baseline		Oral Atorvastatin + IV Normal Saline	2	48 hours	98	9 (9.2)	p=0.50				
Kaya, 2013[56]	SCr ≥0.5 mg/dl or ≥25% from baseline		Oral Rosuvastatin + IV Normal Saline	3		94	5 (5.3)					
Kaya, 2013[56]	SCr ≥0.5 mg/dl from baseline		Oral Atorvastatin + IV Normal Saline	2	48 hours	98	1 (1)	p=NR				
Kaya, 2013[56]	SCr ≥0.5 mg/dl from baseline		Oral Rosuvastatin + IV Normal Saline	3		94	2 (2.1)					
Kaya, 2013[56]	Predictors of CIN, SCr ≥0.5 mg/dl or ≥25% from baseline	LVEF %	Oral Atorvastatin + IV Normal Saline	2	48 hours	98		Multivariate OR: 0.88 (95% CI: 0.77-1.01) p=0.07				
Kaya, 2013[56]	Predictors of CIN, SCr ≥0.5 mg/dl or ≥25% from baseline	LVEF %	Oral Rosuvastatin + IV Normal Saline	3		94						
Kaya, 2013[56]	Predictors of CIN, SCr ≥0.5 mg/dl or ≥25% from baseline	Contrast media (ml)	Oral Atorvastatin + IV Normal Saline	2	48 hours	98		Multivariate OR: 0.1.08 (95% CI: 1.03-1.13) P<0.001				
Kaya, 2013[56]	Predictors of CIN, SCr ≥0.5 mg/dl or ≥25% from baseline	Contrast media (ml)	Oral Rosuvastatin + IV Normal Saline	3		94						

Evidence Table E-20. Contrast induced nephropathy outcomes in studies comparing statin plus IV saline versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Li, 2014[73]	increase in serum creatinine (SCr) of > 0.5 mg/dl or >25% from baseline		Standard atorvastatin + probucol dose	1	24 hours	55	1 (1.8)	p=NR				
Li, 2014[73]	increase in serum creatinine (SCr) of > 0.5 mg/dl or >25% from baseline		Large atorvastatin + probucol dose	2		79	1 (1.3)					
Li, 2014[73]	increase in serum creatinine (SCr) of > 0.5 mg/dl or >25% from baseline		Large atorvastatin dose	3		74	0					
Liu, 2014[74]	Incidence of CIN		Risovustatin	2	72 hours		(5.9)	P=0.68				
Liu, 2014[74]	Incidence of CIN		Atorvastatin	3	72 hours		(5.2)					
Ozhan, 2010[88]	Incidence of CIN		NAC + IV normal saline	2	48 hours	70	7 (10)	p=0.135				
Ozhan, 2010[88]	Incidence of CIN		NAC + Atorvastatin +IV normal saline	3		60	2 (3.3)					
Quintavalle, 2012[92]	Increase in serum creatinine >0.5mg.dl		NAC + IV NaHCO3	2	48 hours	208	16 (7.7)	p=0.085				
Quintavalle, 2012[92]	Increase in serum creatinine >0.5mg.dl		Atorvastatin + NAC + IV NaCO3	3		202	7 (3.5)					

Evidence Table E-20. Contrast induced nephropathy outcomes in studies comparing statin plus IV saline versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Quintavalle, 2012[92]	Increase in serum creatinine >25% from baseline		NAC + IV NaHCO3	2	48 hours	208	14 (7)	p=0.10				
Quintavalle, 2012[92]	Increase in serum creatinine >25% from baseline		Atorvastatin + NAC + IV NaCO3	3		202	6 (3)					
Qiao, 2015[91]	Incidence of CIN		IV saline	1	72 hours	60	2 (0.03)	P=NR				
Qiao, 2015[91]	Incidence of CIN		Rosuvastatin + IV Saline	2		60	2 (0.03)					
Sanei, 2014[98]	Incidence of CIN		Placebo	1	72 hours	NR		P=0.535				
Sanei, 2014[98]	Incidence of CIN		Atorvatatin	2		NR						
Shehata, 2015[102]	Incidence of CIN		IV saline + oral NAC	1	72 hours	65	13 (20)	P<0.05				
Shehata, 2015[102]	Incidence of CIN		Atorvastatin + IV saline + oral NAC	2		65	5 (7.7)					
Toso, 2010[109]	Incidence of CIN, primary definition		Placebo + IV normal saline + NAC	1	5 days		16 (11)	p=0.86				
Toso, 2010[109]	Incidence of CIN, primary definition		atorvastatin + IV normal saline + NAC	2			15 (10)					
Toso, 2010[109]	Incidence of CIN, secondary definition		Placebo + IV normal saline + NAC	1	5 days	152	(15)	p=0.67				
Toso, 2010[109]	Incidence of CIN, secondary definition		atorvastatin + IV normal saline + NAC	2		152	(17)					

Evidence Table E-20. Contrast induced nephropathy outcomes in studies comparing statin plus IV saline versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Toso, 2010[109]	incidence of CIN	Age >=75 years	Placebo + IV normal saline + NAC	1	5 days	97	12 (12)	p=0.98				
Toso, 2010[109]	incidence of CIN	Age >=75 years	atorvastatin + IV normal saline + NAC	2		80	10(13)					
Toso, 2010[109]	Incidence of CIN	High-very High CIN risk score (>=11)	Placebo + IV normal saline + NAC	1	5 days	65	4 (6)	p=0.63				
Toso, 2010[109]	Incidence of CIN	High-very High CIN risk score (>=11)	atorvastatin + IV normal saline + NAC	2		57	6 (11)					
Toso, 2010[109]	Incidence of CIN	LVEF <40%	Placebo + IV normal saline + NAC	1	5 days	49	10 (20)	p=0.37				
Toso, 2010[109]	Incidence of CIN	LVEF <40%	atorvastatin + IV normal saline + NAC	2		41	4 (10)					
Xinwei, 2009[116]	postprocedure increase in serum creatinine of >/= 44.2 umol/L (0.5 mg/dl) or >25% from baseline		Simvastatin 20mg + IV NS	2	24 hours	115	16 (13.9)	p<0.5	48 hours	115	18 (15.7)	p<0.5
Xinwei, 2009[116]	postprocedure increase in serum creatinine of >/= 44.2 umol/L (0.5 mg/dl) or >25% from baseline		Simvastatin 80mg + IV NS	3	24 hours	113	6 (5.3)			113	6 (5.3)	

Evidence Table E-20. Contrast induced nephropathy outcomes in studies comparing statin plus IV saline versus IV saline with or without placebo that are not included in the meta-analysis (continued)

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Yun, 2014[118]	Incidence of CIN		IV normal saline	1	72 hours	416	(18.8)	P=0.040				
Yun, 2014[118]	Incidence of CIN		Risovustatin + IV normal saline	2		408	(13.5)					
Zhang, 2015[119]	Incidence of CIN (moderate dose)		Placebo	1	72 hours	355	16 (4.5)	P=0.029				
Zhang, 2015[119]	Incidence of CIN (moderate dose)		Rosuvastatin	2		357	6 (1.7)					
Zhang, 2015[119]	Incidence of CIN (high dose)		Placebo	1	72 hours	102	4 (3.9)	P=0.834				
Zhang, 2015[119]	Incidence of CIN (high dose)		Rosuvastatin	2		118	4 (3.4)					

%=percent; CI=confidence interval; CIN=contrast induced nephropathy; CRF=chronic renal failure; GFR=glomerular filtration rate; Hrs=hours; LVEF=left ventricular ejection fraction; Mg/dl=milligram per deciliter; Mg=milligram; N=sample size; OR=odds ratio; P=p-value; SCr=serum creatinine; SG=subgroups; Umol/l=micromole per liter

Evidence Table E-21. Summary of other outcomes reported in studies of statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy

Author, yr	Comparisons	Mortality, n/N (%)	Need for RRT, n/N (%)	Other events, n/N (%)
Abaci, 2015[1]	IV normal saline v risovustatin + IV normal saline	NR	NR	Composite outcome: death, nonfatal myocardial infarction, ischemic cerebrovascular accidents, and a decrease in eGFR of _25% or renal failure requiring dialysis, as well as the incidence of the individual components of this composite outcome NS across groups
Acikel, 2010[2]	Arm1: IV Normal Saline Arm2: IV Normal Saline + Oral Atorvastatin Arm3: IV Normal Saline + Chronic Statin Therapy (non-randomized group)	NR	NR	NR
Han, 2013[43]	Arm1: Low-dose Oral Atorvastatin + Oral Probucol Arm2: High-dose Oral Atorvastatin + Oral Probucol Arm3: High-dose Oral Atorvastatin	NR	Need for Dialysis At 48 hours Arm1: 0/54 (0) Arm2: 0/73 (0) Arm3: 0/93 (0) p=NR	NR
Han, 2014[44]	Arm 1: IV normal saline Arm 2: Rosuvastatin + IV normal saline	At 30 days, all cause: Arm1: 5/1500 (.3) Arm2: 3/1498 (.2) P=0.73	At 30 days: Arm1: 2/ 1500 (0.1) Arm2: 0/1498 P=0.5	Worsening heart failure: Arm1: 64/1500 (4.3) Arm2: 39/1498 (2.6) P=0.02
Jo, 2008[51]	Arm 1:Placebo + 0.45% saline Arm 2: simvastatin + 0.45% saline	NR	At 3 days: Arm1: 1/118 (.8) Arm2: 0/118 P=NR[f]	Length of stay: Arm1: 5.1 days Arm2: 4.5 days P=0.39 Composite outcome: Arm1: 5/123 (4.1) Arm2: 3/124 (2.4) P=0.498[c]

Evidence Table E-21. Summary of other outcomes reported in studies of statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy (continued)

Author, yr	Comparisons	Mortality, n/N (%)	Need for RRT, n/N (%)	Other events, n/N (%)
Jo, 2014[53]	Arm1: Regular Atorvastatin dose Arm2: High Atorvastatin dose	At 1 month, overall deaths: Arm1: 1/108 (1.0) Arm2: 2/110 (2.1) p=NR At 6 months, overall deaths: Arm1: 2/108 (2.2) Arm2: 3/110 (3.1) p=NR	Dialysis, at 1 month: Arm1: 0/108 (0) Arm2: 0/110 (0) p=NR Dialysis, at 6 months: Arm1: 0/108 (0) Arm2: 0/110 (0) p=NR	Heart Failure, at 1 month Arm1: 2/108 (2) Arm2: 0/110 (0) p=NR Heart Failure, at 6 months Arm1: 3/108 (3.3) Arm2: 0/110 (0) p=NR Target revascularization (TVR), at 1 month Arm1: 1/108 (1) Arm2: 0/110 (0) p=NR Target revascularization (TVR), at 6 months Arm1: 2/108 (2.2) Arm2: 0/110 (0) p=NR Myocardial Infarction, at 1 month: Arm1: 0/108 (0) Arm2: 0/110 (0) p=NR Myocardial Infarction, at 6 months: Arm1: 0/108 (0) Arm2: 0/110 (0) p=NR
Kaya, 2013[56]	Arm1: Oral Atorvastatin + IV Normal Saline Arm2: Oral Rosuvastatin + IV Normal Saline	NR	NR	NR
Leoncini, 2014[71]	Arm1: No Rosuvastatin Arm2: Rosuvastatin	At 30 days, overall deaths: Arm1: 3/252 (1.2) Arm2: 2/252 (0.8) p=0.9	Dialysis, at 30 days: Arm1: 2/252 (0.8) Arm2: 0/252 (0) p=0.5	Myocardial Infarction, at 30 days: Arm1: 5/22 (2) Arm2: 2/252 (0.8) p=0.45
Li, 2012 [72]	Arm 1: Placebo + IV normal saline Arm 2: Atorvastatin + IV normal saline	NR	NR	Elevated ALT: Arm1: NR (1.2) Arm2: NR (3.85) P=0.57

Evidence Table E-21. Summary of other outcomes reported in studies of statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy (continued)

Author, yr	Comparisons	Mortality, n/N (%)	Need for RRT, n/N (%)	Other events, n/N (%)
Li, 2014[73]	Arm1: Standard Atorvastatin + Probucol Arm2: Large Atorvastatin + Probucol dose Arm3: Large Atorvastatin dose	NR	NR	NR
Liu, 2014[74]	Rosuvastatin vs Atorvastatin	No differenc p=0.141	No difference)p=0.63	HF: no difference
Ozhan, 2010[88]	Arm 2: NAC + IV normal saline Arm 3: NAC + Atorvastatin +IV normal saline	NR	NR	NR
Patti, 2011[89]	Arm 1: Placebo Arm 2: Atorvastatin	NR	NR	Length of stay:[b] Arm1: 3.2 +/-.8 days Arm2: 2.9 +/-.9 days P=0.007 Acute renal failure Arm1: 1/121 (0.8) Arm2: 0/120 (0) P=nr
Qiao, 2015[91]	NR	NR	NR	NR
Quintavalle, 2012[92]	Arm 2: NAC+ IV $NaHCO_3$ Arm 3: Atorvastatin + NAC + IV $NaHCO_3$	At 1 year, whole population: 29/402(7)	At 1 year, whole population: 8/402(2)	Majpr adverse events (not defined) At 24 hours post procedure 9/45 (20) patients with CIAKI 28/357 (7.8) patients without CIAKI
Sanei, 2014[98]	Placbo vs Atorvastatin	NR	NR	NR
Shehata, 2015[102]	NR	NR	None required in either group	Cardiac: none reported in either group
Toso, 2010[109]	Arm 1: Placebo + IV normal saline + NAC Arm 2: atorvastatin + IV normal saline + NAC	Arm1: 0/152 (0) Arm2: 1/152 (0.6) P=NR	Arm1: 1/152 (0.6) Arm2: 0/152 (0) P=NR[f]	NR
Xinwei, 2009[116]	Arm 2: Simvastatin 20mg + IV normal saline Arm 3: Simvastatin 80mg + IV normal saline	NR	NR	Acute renal failure at 24 hours: Arm1: 1/115 Arm2: 0/113 P=NR
Yun, 2014[118]	Iv saline vs Rosuvatatin + IV saline	NR	NR	NR
Zhang, 2015[119]	NR	NR	NR	NR

Evidence Table E-21. Summary of other outcomes reported in studies of statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy (continued)

%=percent; ALT=alanine aminotransferase; CIN=contrast induced nephropathy; Mg/dl=milligram per deciliter; Mg=milligram; Cr= creatinine; N=sample size; NAC=N-acetylcysteine; NaHCo3=sodium bicarbonate; NR=not reported; NS=normal saline; P=p-value; RRT=renal replacement therapy; vs.=versus

* p values associated with chi square tests unless otherwise specified
† Specific error estimation, mean (standard error) vs. mean (standard deviation), not reported
‡ Fisher's exact
§ Multiple comparisons (% placebo vs. % simvastatin) reported: non diabetes, (1.1 vs. 1.2, p value=1.0); Dose of CM≥140 ml, (6.0 vs. 1.7, p value=.369); dose of CM< 140ml, (0 vs. 4.1, p value=.498); LVEF≤40 ml, (2 vs. 0, p value=.476); LVEF>40%(18.2 vs. 0, p value=1.0); Age≥75 years, (6.3 vs. 6.3, p value=1.0); Age < 75 y, (2.9 vs. 2.0, p value=.068)
¶ Composite outcome of death, myocardial infarction, revascularization, cerebral infarction, and dialysis [f]defined as NYHA classification (class change ≥1)
‖ Fisher's exact calculated as p value=1.0 for both comparisons
n/N refers to number of events divided by number at risk.

Evidence Table E-22. Reported adverse events in studies comparing statins plus IV fluids versus IV fluids with or without placebo for the prevention of contrast-induced nephropathy

Author, Year	Adverse events
Abaci, 2015[1]	NR
Acikel, 2010[2]	NR
Han, 2013[43]	NR
Han, 2014[44]	NR
Jo, 2008[51]	NR
Jo, 2014[53]	NR
Kaya, 2013[56]	NR
Leoncini, 2014[71]	NR
Li, 2012 [72]	NR
Li, 2014[73]	NR
Liu, 2014[74]	NR
Ozhan, 2010[88]	NR
Patti, 2011[89]	NR
Qiao, 2015[91]	NR
Quintavalle, 2012[92]	NR
Sanei, 2014[98]	NR
Shehata, 2015[102]	NR
Toso, 2010[109]	NR
XinWei, 2010[116]	Postprocedureal acute renal failure defined as a rapid decrease in renal glomerular filtration with a >176.8 umol/L (2 mg/dl)creatinine increase from baseline. No postprocedural acute renal failure occurred in the S80 group compared with 1 case of renal failure in the S20 group at 24 hours after PCI.
Yun, 2014[118]	NR
Zhang, 2015[119]	NR

Evidence Table E-23. Summary of studies comparing adenosine antagonists versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparisons	N	Population	Age, Range of means§	No. female (%)‡	Mean followup	CM route	Definition of CIN*	Study limitations†
Baskurt, 2009[13]	IV normal saline vs NAC + IV normal saline vs NAC + theophylline + IV normal saline	217	Moderate CKD: eGFR 30-60 ml/min	67.1-67.9	87 (67)	48 hour (short term)	LOCM Ioversol IA	A2	H
Bilasy, 2012[16]	IV normal saline vs theophylline + IV normal saline	60	At least moderate risk for CIN (defined by the Mehran risk score)	56.8-57.2	24 (40)	72 hours	LOCM Iopamidol IA	A3	L
Demir, 2008[31]	IV normal saline vs NAC + IV normal saline vs misopristol + IV normal saline vs theophylline + IV normal saline vs nifedipine + IV normal saline	97	General (non-diabetic)	24-85	43 (45)	Within 3 days	LOCM Iomeprol, Iopamidol IV	A2	H
Kinbara, 2010[62]	IV normal saline vs aminophylline + IV normal saline vs NAC + IV normal saline	45	Stable coronary artery disease	70-71	17 (37)	48 hours	LOCM Iopamidol IA	A2	M
Matejka, 2010[81]	IV normal saline vs theophylline + IV normal saline (all participants had unrestricted oral fluid intake)	56	Cr >1.47mg/dl	75	22 (39)	48 hours CIN 86 hours SrCr	LOCM Iodixanol IA	A3	M

%=percent; CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; F=female; IA=Intrartieral; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low osmolar contrast media; mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NS=normal saline; vs.=versus; Cr=creatinine

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table E-24. Contrast induced nephropathy outcomes in a study comparing adenosine agonists versus other interventions for the prevention of contrast induced nephropathy and other outcomes that is not included in the meta-analysis

Author, year	Measure	SG	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Baskurt, 2009[13]	Creatinine		IV normal saline Hydration	1	48 hours	72	5 (6.9)	All arms p=0.033				
Baskurt, 2009[13]	Creatinine		IV normal saline Hydration + N-acetylcysteine	2		73	7 (9.6)					
Baskurt, 2009[13]	Creatinine		IV normal saline Hydration + N-acetylcysteine + theophylline	3		72	0 (0)					

Evidence Table E-25. Summary of all outcomes reported in studies using adenosine antagonists versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparisons	Mortality (in hospital) n/N(%)	Need for RRT n/N(%)‖	Other events n/N(%)
Baskurt, 2009[13]	Arm 1: IV normal saline Arm 2: NAC + IV normal saline Arm 3: NAC + theophylline + IV normal saline	0 (-)	0 (-)	0 (-)
Bilasy, 2012[16]	Arm 1: IV normal saline Arm 2: theophylline + IV normal saline	NR	NR	Cardiac death: 0 (-) Myocardial infarction: 0 (-)
Demir, 2008[31]	Arm 1: IV normal saline Arm 2: NAC + IV normal saline Arm 3: Misopristol + IV normal saline Arm 4: Theophylline + IV normal saline Arm 5: Nifedipine + IV normal saline	NR	0 (-)	Prolonged hospitalization due to azotemia: 0 (-)
Kinbara, 2010[62]	Arm 1: IV normal saline Arm 2: Aminophylline + IV normal saline Arm 3: NAC + IV normal saline	NR	NR	NR
Matejka, 2010[81]	Arm 1:IV NS Arm 2: theophylline + IV normal saline	0 (-)	0 (-)	Drug side effect: 0 (-) Worsening heart failure requiring IV diuretic : ¶ 3/56 (5.3)

%=percent; CIN=contrast induced nephropathy; N=sample size; NAC=N-acetylcysteine; NR=not reported; NS=normal saline; RRT=renal replacement therapy; vs.=versus

* p values associated with chi square tests unless otherwise specified
†Not specified
‡Calculated chi square=12.63, 4df, Yates corrected p value =.11
§calculated Fisher's exact p value>0.99
¶outcome by intervention arm not reported
‖n/N; number of events/population at risk (patients in arm)

Evidence Table E-26. Adverse events in studies comparing adenosine agonists versus other interventions for the prevention of contrast induced nephropathy and other outcomes

Author, Year	Adverse events
Baskurt, 2009[13]	no cardiac events reported
Bilasy, 2012[16]	no major cardiac events
Demir,2008[31]	no need for RRT or prolonged hospital stay
Kinbara, 2010[62]	none reported
Matejka, 2010[81]	Fluid overload: Adequate hydration was accompanied by mildly elevated LVEDP in both treatment groups (17±11 and 15±8 mmHg; p=0.43); Heart failure: Worsening heart failure requiring IV diuretic treatment during infusion therapy appeared in 3(5.3%) patients and did not require intubation and/or artificial ventilation; Anaphalaxis; Other; No patient died and no patient required temporary or permanent renal replacement therapy during the study course. No adverse events related to the study drug or side effects of it were detected.

g/kg/day=gram per kilogram per day; LVEDP=left ventricular ejection diastolic pressure; min=minute; mmHG=millimeter of mercury; NaCl=sodium chloride; NR=not reported

Evidence Table E-27. Summary of studies assessing the use of hemodialysis or hemofiltration for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	CKD stages inclusion criteria, mean/range	Age, range of means‡	Mean followup	Procedure	CM	Definition of CIN*	Study limitations†
Frank, 2003[36]	IV normal saline vs. IV normal saline + hemodialysis	17	Inclusion Cr ≥.3 mg/dl Range CrCl: 9.8-29.6 mL/min Stages 4-5	47-76	8 weeks	Coronary angiography	LOCM Iomeprol	NR	H
Katoh, 2014[55]	No Right Atrium Hemodiafiltration vs. Right Atrium Hemodiafiltration	66	eGFR <45 ml/min/1.73m^2	75-80	1 month	CAG or PCI	LOCM Iopamidol	B2	H
Lehnert, 1998[70]	IV normal saline vs IV normal saline + hemodialysis	30	Inclusion Cr >1.4 mg/dl Mean Cr: 2.4 + /- 0.16 mg/dl CrCl not given	60-63.3	14 days	Angiography (27 coronary, 2 peripheral arterial, 1 venous)	LOCM Iopentol	A2	H
Marenzi, 2003[77]	IV normal saline vs. hemofiltration	114	Inclusion Cr >2.0 mg/dl Mean CrCl: 26 + /- 9 ml/min Stages 3-4	58-80	12 months	Elective coronary interventions	LOCM Iopentol	A1	H
Marenzi, 2006[79]	IV normal saline vs. hemofiltration post CM + IV normal saline vs. hemofiltration pre/post CM + IV normal saline	92	Inclusion CrCl ≤ 30 mL/min Range CrCl: 14-30 mL/min Stages 4-5	71-72	21 days	Elective diagnostic and therapeutic coronary interventions	LOCM Iopentol	A2	M
Reinecke, 2007[95]	IV normal saline + glucose vs. IV normal saline + glucose + hemodialysis vs. IV normal saline + glucose + NAC	424	Inclusion Cr ≥1.3 mg/dl and ≤ 3.5 mg/dl Median GFR 46.6 and 49.3 Stage 3	66-67.9	Median 553 Days Range 63-1316 days)	Elective left heart catheterization	LOCM Iopromide	A2	H
Vogt, 2001[113]	Saline (not specified) vs. Saline (not specified) + hemodialysis	113	Inclusion Cr >2.3 mg/dl Range CrCl: 13-30 mL/min Stages 4-5	59-80	NR	Renal angioplasty Peripheral angioplasty Coronary angiography Computed tomography	LOCM	A3	H

CKD=Chronic Kidney Disease; CM=contrast media, CIN=contrast induced nephropathy; Cr=creatinine; CrCl=creatinine clearance; IV=intravenous; LOCM=low-osmolar contrast media; NAC=N-acetylcysteine; NR=not reported; PCI=Percutaneous coronary intervention; RCT=Randomized Controlled Trial

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), >25%(B1); ≥0.3 mg/dl or ≥25%(B2) reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table E-28. Contrast-induced nephropathy outcomes in a study comparing renal replacement therapy versus other interventions for the prevention of contrast-induced nephropathy nephropathy and other outcomes that is not included in the meta-analysis

Author, year	Measure	SG	Intervention	ARM	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1	Time Point 2	Time point 2 N anlyzed	n (%) with outcome at timepoint 2	Comparison statistics at time point 2
Katoh, 2014[55]	increase of SCr ≥0.3 mg/dl, ≥ 25 % from the baseline value within 1 week after the administration of contrast medium		No Right Atrium Hemodiafiltration	1	1 week	41	11 (27)	p=0.26				
Katoh, 2014[55]	increase of SCr ≥0.3 mg/dl, ≥ 25 % from the baseline value within 1 week after the administration of contrast medium		Right Atrium Hemodiafiltration	2		25	3 (12)					
Marenzi, 2003[77] Should be with RRT	12-month mortality		Saline	1	12 months	48	9 (cumulative 1-year mortality: 30%)	p=0.1				
Marenzi, 2003[77]	12-month mortality		Hemofiltration	2		57	5 (cumulative 1-year mortality: 10%)					
Marenzi, 2006[79]	greater than 25% increase in Cr from baseline		isotonic saline	1	9 days	30	12 (40)	All arms p=0.013				
Marenzi, 2006[79] (continued)	greater than 25% increase in Cr from baseline		isotonic saline + hemofiltration post contrast	2		31	8 (26)					
Marenzi, 2006[79]	greater than 25% increase in Cr from baseline		isotonic saline + hemofiltration pre and post contrast	3		31	1 (3)					

%=percent; A1=arm 1; A2=arm 2; A3=arm 3; BL=blood level; CI=confidence interval; CIN=contrast induced nephropathy; CKD=chronic kidney disease; Cr=creatinine; GFR=glomerular filtration rate; H=hour; Mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NS=non-significant; OR=odds ratio; P=p-value; SCr=serum creatinine; Umol/l=micromole per liter

Evidence Table E-29. Summary of all outcomes reported on use of hemodialysis or hemofiltration for the prevention of contrast-induced nephropathy

Author, year	Comparison	Mortality n/N (%)	Need for RRT n/N (%)	Other events n/N (%)
Frank, 2003[36]	Arm 1: IV normal saline Arm 2: IV normal saline + hemodialysis	NR	Long-term Arm1: 1 (10%) (pulmonary edema) Arm2: 1 (10%) (uremic pericarditis) P=1.0	Pulmonary edema at 6 hours Arm1: 1 (10%) Arm2: 0 (-) P=NS
Katoh, 2014[55]	Arm1: No Right Atrium Hemodiafiltration Arm2: Right Atrium Hemodiafiltration	NR	1 month Arm1: 0/41 (0) Arm2: 0/25 (0) p=NR	NR
Lehnert, 1998[70]	Arm 1: IV normal saline Arm 2: IV normal saline + hemodialysis	NR	NR	NR
Marenzi, 2003[77]	Arm 1: IV normal saline Arm 2: hemofiltration	In-hospital mortality Arm1: 8 (14%) Arm2: 1 (2%) P=0.02	Emergency HD Arm1: 10 (18%) Arm2: 0 (-) P< 0.001 Long-term Arm1: 14 (25%) Arm2: 2 (3%) P<0.001	MI Arm1: 3 (5%) Arm2: 1 (2%) P=0.36 Pulmonary edema Arm1: 6 (11%) Arm2: 0 (-) P=0.02
Marenzi, 2006[79]	Arm 1: IV normal saline Arm 2: IV normal saline + hemofiltration post CM Arm 3: IV normal saline + hemofiltration pre/post CM	In-hospital mortality	Arm1: 9 (30%) Arm2: 3 (10%) Arm3: 0 (-) P=0.002	NR

Evidence Table E-29. Summary of all outcomes reported on use of hemodialysis or hemofiltration for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality n/N (%)	Need for RRT n/N (%)	Other events n/N (%)
Reinecke, 2007[95]	Arm 1: IV normal saline + glucose Arm 2: IV normal saline + glucose + hemodialysis + Arm 3: IV normal saline+ glucose + NAC	In-hospital mortality Arm1: 1 (0.7%) Arm2: 3 (2.2%) Arm 3: 1 (0.7%) P=0.427 30-day mortality Arm1: 3 (2.2%) Arm2: 3 (2.2%) Arm 3: 1 (0.7%) P=0.540 Long-term mortality (deaths per 100 patient-years) Arm1: 9.7 Arm 2: 13.1 Arm 3: 9.9 P=0.582	In-hospital Arm1: 1 (0.7%) Arm2: 2 (1.5%) Arm 3: 1 (0.7%) P=0.762	Hematomas Arm1: 1 (0.7%) Arm 2: 5 (3.7%) Arm 3: 5 (3.6%) P=0.226
Vogt, 2001[113]	Arm 1: Saline (not specified) Arm 2: Saline (not specified) + hemodialysis	Arm1: 1 (2%) Arm2: 1 (2%) P=1.0 Time of death=NS	Before day 6 Arm1: 3 (5%) Arm2: 8 (15%) P=0.12 Before day 6 Arm1: 2 (4%) Arm2: 4 (7%) P=0.44	MI Arm1: 2 (4%) Arm2: 2 (4%) P=1.0 Stroke Arm1: 0 (-) Arm2: 2 (4%) P=0.24 Pulmonary edema Arm1: 4 (7%) Arm2: 1 (2%) P=0.36

CM=contrast media; CrCl=creatinine clearance; HD-hemodialysis; HF=hemofiltration; IV=intravenous; MI=myocardial infarction; NAC=N-acetylcysteine; NS=not significant; RRT=renal replacement therapy

*n/N; number of events/population at risk (patients in arm)

Evidence Table E-30. Adverse events in studies comparing replacement therapy versus other interventions for the prevention of contrast-induced nephropathy

Author, Year	Adverse events
Frank, 2003[36]	Fluid overload: One participant in the control group developed respiratory insufficiency with pulmonary edema 6 hours after angiography and needed artificial ventilation for 30 hours.; Heart failure; Anaphalaxis; development of ESRD: One patient in each group developed ESRD at 8 weeks.; oliguria or anuria: No patient in either group developed these conditions at 1 week. One participant in each group underwent coronary artery bypass surgery; both were anuric after the cardiac surgery.
Katoh, 2014[55]	One patient with Ci-AKI died due to sepsis 19 months after procedure
Marenzi, 2003[77]	pulmonary edema:6 in the control group0 in the HF group(P 0.02); Heart failure; Anaphalaxis; treatment associated hypotension (in text); hypotension or shock (in the table): In the text: no treatment-associated hypotension in HF group (one participant developed shock two days at the end of the hemofiltration treatment)In the table: "hypotension or shock" in 3 participants in the control group and 1 in the HF group (P 0.36); Bleeding at site of vascular access: 3 patients in the HF group Another AE: "blood transfusion required"(in table). 3 in control group and 1 in HF group (P 0.36); myocardial infarction: control group: 2 Q wave and 1 non-Q wave HF group: 1 Q wave and 1 non-Q wave (this information is in a table)Also: high-rate atrial fibrillation with hemodynamic instability1 patient in the HF group; none mentioned in the control group
Marenzi, 2006[79]	Acute myocardial infarction: 5 cases in the control group, 4 in the post hemofiltration and 1 in pre/post hemofiltration; Cardiogenic shock requiring intra-aortic balloon pump: 1 case in the control group and none in the other 2 groups; Blood transfusion: 4 cases in the control group, 6 in the post hemofiltration and 5 in pre/post hemofiltration
Reinecke,2007[95]	adverse events reported as secondary outcome.
Vogt, 2001[113]	Table 3 lists clinical events, though most of these were actually outcomes. The additional AEs are: HD-related complications (AV formation): 2 of the 55 HD patients (4%) (none in the non-HD group). P 0.24

AE=adverse event; ESRD=end stage renal disease; HD=hemodialysis; HF=hemofiltration; NR=not reported

Evidence Table E-31. Summary of the characteristics and outcomes of studies comparing ascorbic acid and other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	N	Population	Age, range of mean §	No. female (%)‡	Mean follow up	CM Route*	Definition of CIN*	Study limitations†
Albabtain, 2013[4]	IV Normal Saline vs. Oral Ascorbic Acid + IV Normal Saline vs. Oral NAC + IV Normal Saline vs. Oral NAC + Oral Ascorbic Acid + IV Normal Saline	243	SrCr ≥1.3 mg/dl or on diabetes medication	61	66 (27)	4-5 days	LOCM (Ioxaglate) IA	A3	L
Boscheri, 2007[18]	Placebo + IV Normal Saline vs. Oral Ascorbic Acid + IV Normal Saline	143	Chronic renal failure and stable SrCr >120 umol/l	71	40 (28)	6 days	IOCM (Iodixanol) IA	A1	L
Brigouri, 2007[22]	IV Normal Saline + oral NAC vs. IV NaHCO3 + oral NAC vs. IV Normal Saline + IV ascorbic acid + oral NAC	326	CKD with stable Cr at 2.0 mg/dL and/or estimated glomerular filtration rate 40	70	61 (19)	7 days	IOCM (Iodixanol) IA	A1	L
Brueck, 2013[23]	Placebo + IV Normal Saline vs. NAC + IV Normal Saline vs. Ascorbic Acid + IV Normal Saline	499	SrCr ≥1.3 mg/dl	75	181 (36)	72 hours	LOCM (NR) IA	A3	L
Dvorsak, 2013[33]	IV Normal Saline + placebo vs. IV Normal Saline + ascorbic acid	81	Stable serum creatinine >107 umol/L	71	22 (27)	4 Days	LOCM (Iopamidol) IA	A1	M
Jo, 2009[52]	Oral NAC + IV 0.45% Saline vs. Oral Ascorbic acid + IV 0.45% Saline	212	CrCl ≤60 ml/min or SrCr ≥1.1 mg/dl	65	47 (22)	6 months	IOCM (Iodixanol) IA	A3	L
Spargias, 2004[103]	Placebo + IV Normal Saline vs. Oral Ascorbic Acid + IV Normal Saline	231	SrCr ≥1.2 mg/dl	64-67	18 (8)	5 days	LOCM/IOCM (NR) IA	A3	L
Zhou, 2012[120]	IV Normal Saline vs. IV and Oral Ascorbic Acid + IV Normal Saline	156	eGFR <60 ml/min/1.73 m^2 or SrCr ≥1.1 mg/dl	71	58 (37)	2 days	LOCM (Iopromide, Iohexol) IOCM (Iodixanol) IA	A3	M

Evidence Table E-31. Summary of the characteristics and outcomes of studies comparing ascorbic acid and other interventions for the prevention of contrast-induced nephropathy (continued)

CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; Cr=creatinine; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; IA=intra-arterial; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low-osmolar contrast media; mg/dl=milligram per deciliter; ml/min/1.73m^2=millimeter per minute per 1.73 meter squared; ml/min=milliliter per minute; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; No.=number of; NR=not reported; SrCr=serum creatinine; umol/l=micromole per liter

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table E-32. Contrast induced nephropathy outcomes in studies comparing of ascorbic acid and other interventions that are not included in the meta-analysis

Author, year	Measure	Sub-group	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1
Briguori, 2007[22]	≥25% increase in SrCr from baseline		Saline plus NAC	2	48 hours	111	11 (9.9)	p=0.01
Briguori, 2007[22]	≥25% increase in SrCr from baseline		Bicarbonate plus NAC	3		108	2 (1.9)	
Briguori, 2007[22]	≥25% increase in SrCr from baseline		Saline plus ascorbic acid plus NAC	4		107	11 (10.3)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours		Oral NAC + IV 0.45% Saline	2	48 hours	83	1 (1.2)	p=0.37
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours		Oral Ascorbic acid + IV 0.45% Saline	3		91	4 (4.4)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CrCl ≤30 ml/min	Oral NAC + IV 0.45% Saline	2	48 hours	12	0 (0)	p=0.123
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CrCl ≤30 ml/min	Oral Ascorbic acid + IV 0.45% Saline	3		7	2 (28.6)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CrCl >30 ml/min	Oral NAC + IV 0.45% Saline	2	48 hours	71	1 (1.4)	p=1.00
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CrCl >30 ml/min	Oral Ascorbic acid + IV 0.45% Saline	3		84	2 (2.4)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Diabetes	Oral NAC + IV 0.45% Saline	2	48 hours	38	0 (0)	p=0.039
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Diabetes	Oral Ascorbic acid + IV 0.45% Saline	3		32	4 (12.5)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Non-diabetic	Oral NAC + IV 0.45% Saline	2	48 hours	45	1 (2.2)	p=0.433
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Non-diabetic	Oral Ascorbic acid + IV 0.45% Saline	3		59	0 (0)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CM ≥140 ml	Oral NAC + IV 0.45% Saline	2	48 hours	62	0 (0)	p=0.245

Evidence Table E-32. Contrast induced nephropathy outcomes in studies comparing of ascorbic acid and other interventions that are not included in the meta-analysis (continued)

Author, year	Measure	Sub-group	Intervention	Arm	Time Point 1	Time point 1 N analyzed	n (%) with outcome at time point 1	Comparison* statistics at time point 1
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CM ≥140 ml	Oral Ascorbic acid + IV 0.45% Saline	3		66	3 (4.5)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CM <140 ml	Oral NAC + IV 0.45% Saline	2	48 hours	21	1 (4.8)	p=1.00
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	CM <140 ml	Oral Ascorbic acid + IV 0.45% Saline	3		25	1 (4.0)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	LVEF ≤40%	Oral NAC + IV 0.45% Saline	2	48 hours	8	0 (0)	p=0.228
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	LVEF ≤40%	Oral Ascorbic acid + IV 0.45% Saline	3		11	3 (27.3)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	LVEF >40%	Oral NAC + IV 0.45% Saline	2	48 hours	45	1 (2.2)	p=0.437
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	LVEF >40%	Oral Ascorbic acid + IV 0.45% Saline	3		58	0 (0)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Age ≥70	Oral NAC + IV 0.45% Saline	2	48 hours	25	0 (0)	p=1.0
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Age ≥70	Oral Ascorbic acid + IV 0.45% Saline	3		26	1 (3.8)	
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Age <70	Oral NAC + IV 0.45% Saline	2	48 hours	58	1 (1.7)	p=0.621
Jo, 2009[52]	≥25% or ≥0.5 mg/dl increase in SrCr from baseline within 48 hours	Age <70	Oral Ascorbic acid + IV 0.45% Saline	3		65	3 (4.6)	

%=percent; CM=contrast media; CrCl=creatinine clearance; IV=intravenous; LVEF=left ventricular ejection fraction; mg/dl=milligram per deciliter; ml/min=millimeter per minute; ml=millimeter; N=sample size; NAC=N-acetylcysteine; p=p-value; SrCr=serum creatinine

Evidence Table E-33. Summary of other outcomes reported in studies comparing ascorbic acid and other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Albabtain, 2013[4]	Arm1: IV Normal Saline Arm2: Oral Ascorbic Acid + IV Normal Saline Arm3: Oral NAC + IV Normal Saline Arm4: Oral NAC + Oral Ascorbic Acid + IV Normal Saline	NR	NR	NR	NR
Boscheri, 2007[18]	Arm1: Placebo + IV Normal Saline Arm2: Oral Ascorbic Acid + IV Normal Saline	NR	NR	NR	NR
Brigouri, 2007[22]	Arm1: IV Normal Saline + oral NAC Arm2: IV NaHCO3 + oral NAC Arm3: IV Normal Saline + IV ascorbic acid + oral NAC	NR	Temporary Dialysis At 5 days Arm1: 1/111 (0.9) Arm2: 1/108 (0.9) Arm3: 4/107 (3.8) p=NR	NR	NR
Brueck, 2013[23]	Arm1: Placebo + IV Normal Saline Arm2: NAC + IV Normal Saline Arm3: Ascorbic Acid + IV Normal Saline	NR	NR	NR	NR
Dvorsak, 2013[33]	Arm1: IV Normal Saline + placebo Arm2: IV Normal Saline + ascorbic acid	NR	Need for Dialysis At 3-4 days Arm1: 0/41 (0) Arm2: 0/40 (0) p=NR	NR	Heart Failure At 3-4 days Arm1: 13/41 (31.7) Arm2: 15/40 (37.5) p=0.377
Jo, 2009[52]	Arm1: Oral NAC + IV 0.45% Saline Arm2: Oral Ascorbic acid + IV 0.45% Saline	At 1 month Arm1: 2/106 (1.9) Arm2: 1/106 (0.9) p=NR At 6 months Arm1: 2/97 (2.1) Arm2: 2/101 (2.0) p=NR	Need for Dialysis At 1 month Arm1: 1/106 (0.9) Arm2: 1/106 (0.9) p=NR At 6 months Arm1: 1/97 (1) Arm2: 2/101 (2) p=NR	NR	Myocardial Infarction At 1 month Arm1: 1/106 (0.9) Arm2: 3/106 (2.8) p=NR At 6 months Arm1: 1/97 (1) Arm2: 3/101 (3) p=NR

Evidence Table E-33. Summary of other outcomes reported in studies comparing ascorbic acid and other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Spargias, 2004[103]	Arm1: Placebo + IV Normal Saline Arm2: Oral Ascorbic Acid + IV Normal Saline	NR	NR	NR	NR
Zhou, 2012[120]	Arm1: IV Normal Saline Arm2: IV and Oral Ascorbic Acid + IV Normal Saline	NR	NR	Length of Hospitalization Arm1: 5.1 (2.3) Arm2: 4.5 (2.6) p=0.38	Major cardiac events At 2 days Arm1: 0/74 (0) Arm2: 0/82 (0) p=NR

%=percent; IV=intravenous; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; NR=not reported; p=p-value; RRT=renal replacement therapy; SD=standard deviation

Evidence Table E-34. Adverse events in studies comparing ascorbic acid and other interventions for the prevention of contrast induced nephropathy

Author, Year	Adverse events
Albabtain, 2013[4]	NR
Boscheri, 2007[18]	NR
Briguori, 2007[22]	NR
Brueck, 2013[23]	NR
Dvorsak, 2013[33]	NR
Jo, 2009[52]	1 participant experienced cerebral infarction in the NAC arm.
Spargias, 2004[103]	NR
Zhou, 2012[120]	Most AE in study were non-serious and self-resolving.

AE=adverse events; NAC=N-acetylcysteine; NR=not reported

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Appendix F. Study Limitations

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Abaci, 2015[1]	Yes	No	No	Yes	Yes
Abizaid, 1999[2]	Yes	No	No	Yes	Yes
Acikel, 2010[3]	Yes	Yes	Unclear	Yes	Yes
ACT, 2011[4]	Yes	Yes	Yes	Yes	Yes
Adolph, 2008[5]	Yes	Unclear	Yes	Yes	Yes
Albabtain, 2013[6]	Yes	Yes	No	Yes	Yes
Alexopoulos, 2010[7]	Yes	Yes	Yes	Unclear	Yes
Alioglu, 2013[8]	No	No	Yes	Unclear	Yes
Allaqaband, 2002[9]	Yes	Unclear	Unclear	Yes	Yes
Amini, 2009[10]	Yes	Yes	Yes	Unclear	Yes
Aslanger, 2012[11]	Yes	No	No	Yes	Yes
Awal, 2011[12]	Unclear	Unclear	Unclear	Yes	Yes
Azmus, 2005[13]	Yes	Yes	Yes	Yes	Yes
Bader, 2004[14]	Unclear	Unclear	No	Unclear	Unclear
Baker, 2003[15]	Unclear	Unclear	Yes	Yes	Yes
Baranska-Kosakowska, 2007[16]	Unclear	Unclear	Unclear	Yes	Yes
Baskurt, 2009[17]	Unclear	Unclear	Unclear	Yes	Yes
Beyazal, 2014[18]	No	No	No	No	Yes
Bilasy, 2012[19]	Yes	Yes	Yes	Yes	Yes
Boccalandro, 2003[20]	Unclear	Unclear	Unclear	Unclear	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Boscheri, 2007[21]	Unclear	Yes	Yes	Yes	Yes
Boucek, 2013[22]	Yes	Yes	Yes	Yes	Yes
Brar, 2008[23]	Yes	Yes	Yes	Yes	Yes
Brar, 2014[24]	Yes	Yes	Yes	Unclear	Yes
Briguori, 2002[25]	Yes	Unclear	Unclear	Yes	Yes
Briguori, 2004[26]	Unclear	Unclear	Yes	Yes	Yes
Briguori, 2005[27]	Yes	Unclear	Unclear	Yes	Yes
Briguori, 2007[28]	Yes	Yes	Yes	Yes	Yes
Briguori, 2011[29]	Yes	Yes	Yes	Yes	Yes
Brueck, 2013[30]	Yes	Yes	Yes	Yes	Yes
Burns, 2010[31]	Yes	Yes	Unclear	Yes	Yes
Carbonell, 2007[32]	Yes	Yes	Yes	Yes	Yes
Carbonell, 2010[33]	Yes	Yes	Yes	Yes	Yes
Castini, 2010[34]	Yes	Yes	Yes	Unclear	Yes
Chen, 2008[35]	Unclear	Unclear	Unclear	Unclear	Yes
Cho, 2010[36]	Yes	Unclear	Unclear	Yes	Yes
Chousterman, 2011[37]	No	No	No	Yes	Yes
Chousterman, 2013[38]	No	No	No	Yes	Yes
Demir, 2008[39]	No	Unclear	No	No	No
Durham, 2002[40]	Yes	Unclear	Unclear	Yes	Yes
Dvorsak, 2013[41]	Unclear	Unclear	Unclear	Yes	Yes
Erturk, 2014[42]	Yes	Yes	Unclear	Yes	Yes
Ferrario, 2009[43]	Yes	Unclear	Unclear	Yes	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Firouzi, 2012[44]	Yes	Unclear	No	Yes	No
Frank, 2003[45]	No	No	No	Unclear	No
Fung, 2004[46]	Yes	Yes	No	Yes	Unclear
Goldenberg, 2004[47]	Yes	Yes	Yes	Yes	Yes
Gomes, 2012[48]	Yes	Unclear	Unclear	Unclear	Yes
Gulel,2005[49]	Yes	No	Unclear	Yes	Yes
Gunebakmaz, 2012[50]	Unclear	Unclear	Unclear	Yes	Yes
Hafiz, 2012[51]	Yes	Unclear	Unclear	Yes	Yes
Han, 2013[52]	Unclear	Unclear	Unclear	Unclear	Unclear
Han, 2013[53]	Yes	No	No	No	No
Han, 2014[54]	Yes	No	No	No	No
Hans, 1998[55]	Unclear	Unclear	Unclear	Unclear	Unclear
Heguilen, 2013[56]	Unclear	Unclear	Yes	Yes	Yes
Heng, 2008[57]	Unclear	Unclear	Unclear	Yes	Yes
Holscher, 2008[58]	Unclear	Unclear	Unclear	Yes	Yes
Hsu, 2007[59]	Yes	Unclear	Yes	Yes	Yes
Hsu, 2012[60]	No	No	No	Yes	Yes
Huber, 2006[61]	No	No	No	Yes	Yes
Izani Wan Mohamed, 2008[62]	Yes	Yes	Yes	Yes	Yes
Jaffery, 2012[63]	Unclear	Unclear	Unclear	Yes	Yes
Jo, 2008[64]	Yes	Yes	Yes	Unclear	Yes
Jo, 2009[65]	Yes	Unclear	Yes	Yes	Yes
Jo, 2014[66]	Yes	No	No	Yes	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Kama, 2014[67]	Yes	Unclear	Unclear	Yes	No
Kay, 2003[68]	Yes	Yes	Unclear	Yes	Yes
Kaya, 2013[69]	No	No	No	Yes	Yes
Kefer, 2003[70]	Yes	Yes	Yes	Yes	Yes
Khalili, 2006[71]	Unclear	Unclear	Unclear	Unclear	Yes
Kim, 2010[72]	Yes	Unclear	No	Yes	Yes
Kimmel, 2008[73]	Unclear	Unclear	Yes	Yes	Yes
Kinbara, 2010[74]	Yes	Unclear	Unclear	Yes	Yes
Koc, 2013[75]	Yes	Unclear	Unclear	Yes	Yes
Kooiman, 2014[76]	Yes	No	No	Yes	Yes
Kooiman, 2014[77]	No	No	No	Yes	Yes
Kotlyar, 2005[78]	Yes	Unclear	Yes	Yes	Unclear
Kumar, 2014[79]	No	No	No	Unclear	Unclear
Lawlor, 2007[80]	Unclear	Unclear	Yes	Unclear	Yes
Lee, 2011[81]	Yes	Yes	No	Yes	Yes
Lehnert, 1998[82]	Unclear	Unclear	No	Unclear	Unclear
Leoncini, 2014[83]	Yes	Unclear	Unclear	Yes	Yes
Li, 2012[84]	Unclear	Unclear	Yes	Yes	Yes
Li, 2014[85]	No	No	No	No	Yes
Li, 2014[86]	No	No	Unclear	No	Yes
Liu, 2013[87]	No	No	No	No	No
Liu, 2014[88]	No	No	No	No	Yes
MacNeill, 2003[89]	Unclear	Unclear	Yes	Unclear	No

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Maioli, 2008[90]	Unclear	Unclear	Yes	Yes	Yes
Maioli, 2011[91]	Yes	Unclear	Unclear	Yes	Yes
Malhis, 2010[92]	No	No	No	Unclear	Unclear
Manari, 2014[93]	Yes	No	Yes	Yes	Yes
Marenzi, 2003[94]	Yes	Unclear	No	Unclear	Unclear
Marenzi, 2006[95]	Yes	Unclear	Unclear	Yes	Yes
Marenzi, 2006[96]	Yes	Yes	Unclear	Yes	Yes
Masuda, 2007[97]	Yes	Yes	Yes	No	Yes
Matejka, 2010[98]	Yes	Yes	Yes	No	No
Merten, 2004[99]	Yes	Unclear	Yes	Yes	Yes
Miner, 2004[100]	Unclear	Unclear	Unclear	Yes	Yes
Motohiro, 2011[101]	Unclear	Yes	Yes	Yes	Yes
Mueller, 2002[102]	Unclear	Unclear	Yes	Yes	Yes
Ng, 2006[103]	Yes	Unclear	Yes	Yes	Yes
Ochoa, 2004[104]	Unclear	Unclear	Yes	Yes	Yes
Oguzhan, 2013[105]	Yes	Yes	Unclear	Yes	Yes
Oldemeyer, 2003[106]	Yes	Yes	Yes	Yes	Yes
Ozcan, 2007[107]	Unclear	Unclear	Unclear	Yes	Yes
Ozhan, 2010[108]	Yes	Unclear	Unclear	Yes	Yes
Pakfetrat, 2009[109]	Unclear	Unclear	Yes	Yes	Yes
Patti, 2011[110]	Yes	Yes	Yes	Yes	Yes
Poletti, 2007[111]	Yes	Yes	Yes	Yes	Yes
Qiao, 2015[112]	Unclear	Unclear	Unclear	Unclear	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Quintavalle, 2012[113]	Yes	No	No	Yes	Yes
Rashid, 2004[114]	Yes	Yes	Yes	Yes	Yes
Ratcliffe, 2009[115]	Unclear	Unclear	Unclear	Yes	Yes
Recio-Mayoral,2007[116]	Unclear	No	No	Yes	Yes
Reed, 2010[117]	No	No	No	Yes	Yes
Reinecke, 2007[118]	Unclear	Unclear	Unclear	Yes	Yes
Rosenstock, 2008[119]	Yes	No	Unclear	No	Yes
Sadat, 2011[120]	Yes	Unclear	Unclear	Yes	Yes
Sandhu, 2006[121]	Yes	Yes	Unclear	Yes	Yes
Sanei, 2014[122]	Yes	Yes	Yes	Yes	Yes
Sar, 2010[123]	Yes	Unclear	Unclear	Yes	Yes
Seyon, 2007[124]	No	No	No	No	Yes
Shavit, 2009[125]	No	No	Yes	No	Yes
Shehata, 2014[126]	Yes	Yes	Unclear	Yes	Yes
Shehata, 2015[127]	Unclear	Yes	Yes	Yes	Yes
Shyu, 2002[128]	Yes	Yes	Yes	Yes	Yes
Solomon, 1994[129]	Unclear	Unclear	Unclear	Yes	Yes
Spargias, 2004[130]	Yes	Yes	Yes	Yes	Yes
Talati, 2012[131]	No	No	Yes	No	Yes
Tamura, 2009[132]	Yes	Yes	No	Yes	Yes
Tanaka, 2011[133]	No	Unclear	Unclear	Yes	Yes
Tepel, 2000[134]	No	No	No	Yes	Yes
Thayssen, 2014[135]	Yes	Yes	No	Yes	Yes

Author, Year	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?
Thiele, 2010[136]	Yes	No	Unclear	Yes	Yes
Toso, 2010[137]	Yes	Unclear	Unclear	Yes	Yes
Traub, 2013[138]	Unclear	Unclear	Unclear	Yes	Yes
Trivedi, 2003[139]	Unclear	Unclear	No	Yes	Yes
Ueda, 2011[140]	Yes	Unclear	Unclear	Yes	Yes
Vasheghani, 2009[141]	Yes	Yes	Yes	Yes	Yes
Vasheghani-Farahani, 2010[142]	Yes	Yes	Yes	Yes	Yes
Vogt, 2001[143]	No	No	No	No	Unclear
Wang, 2008[144]	Unclear	Unclear	Yes	Yes	Yes
Webb, 2004[145]	Yes	Yes	Yes	Yes	Yes
Wolak, 2013[146]	No	No	No	Yes	Yes
Xinwei, 2009[147]	Yes	No	No	Yes	Yes
Yavari, 2014[148]	Yes	Yes	Unclear	Yes	Yes
Yeganehkhah, 2014[149]	No	No	No	No	No
Yin, 2013[150]	Yes	No	No	Yes	Yes
Yun, 2014[151]	No	No	No	No	Yes
Zhang, 2015[152]	Yes	Unclear	Unclear	Yes	Yes
Zhou, 2012[153]	Unclear	Unclear	Unclear	Yes	Yes

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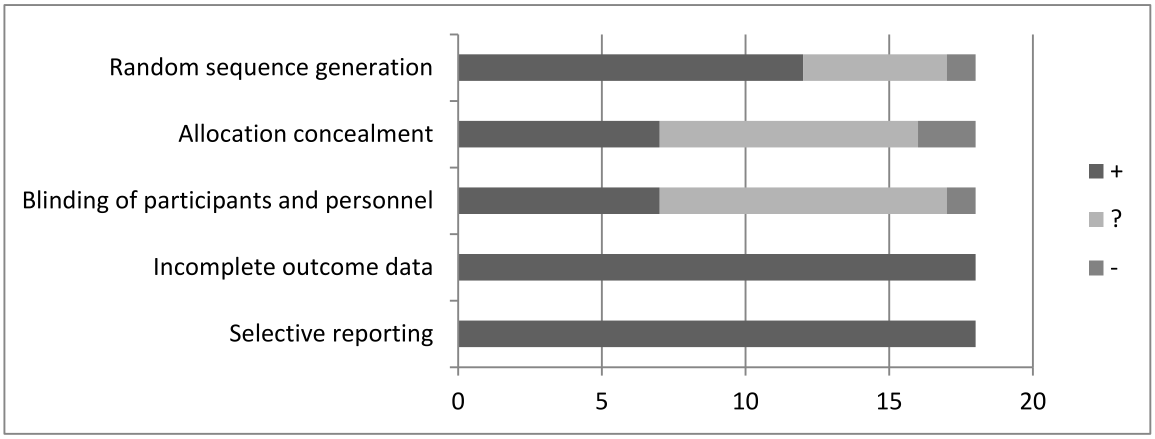
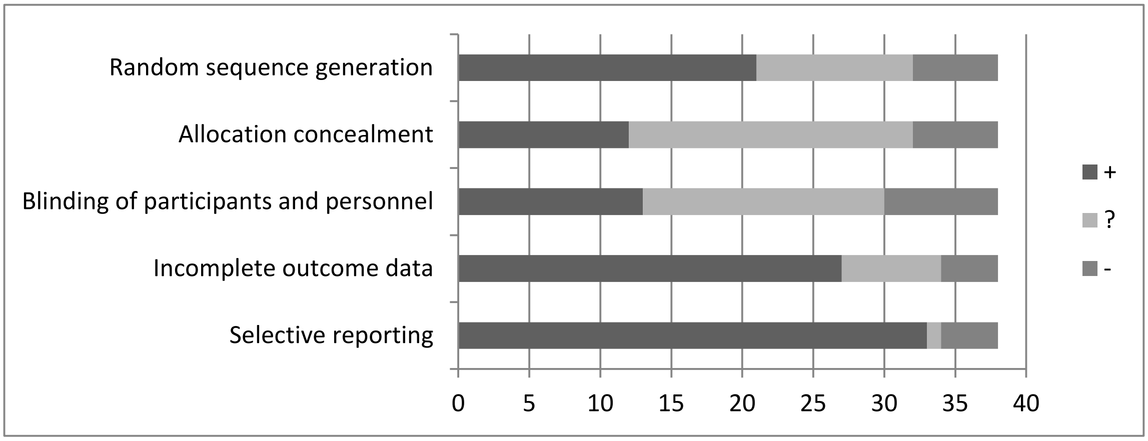
Appendix G. Study Limitation Figures

N-Acetylcysteine versus Intravenous Saline

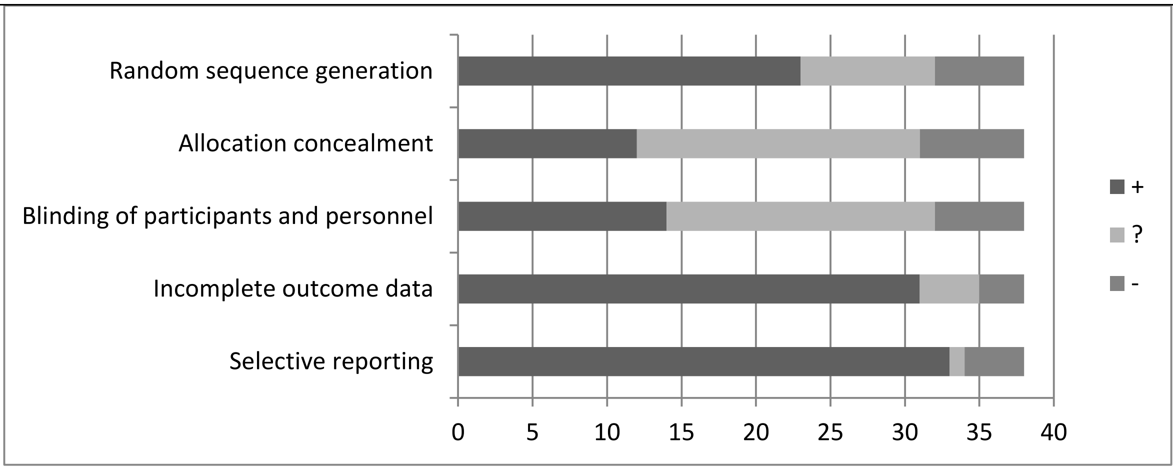
High dose N-acetylcysteine versus IV saline (CIN outcomes)



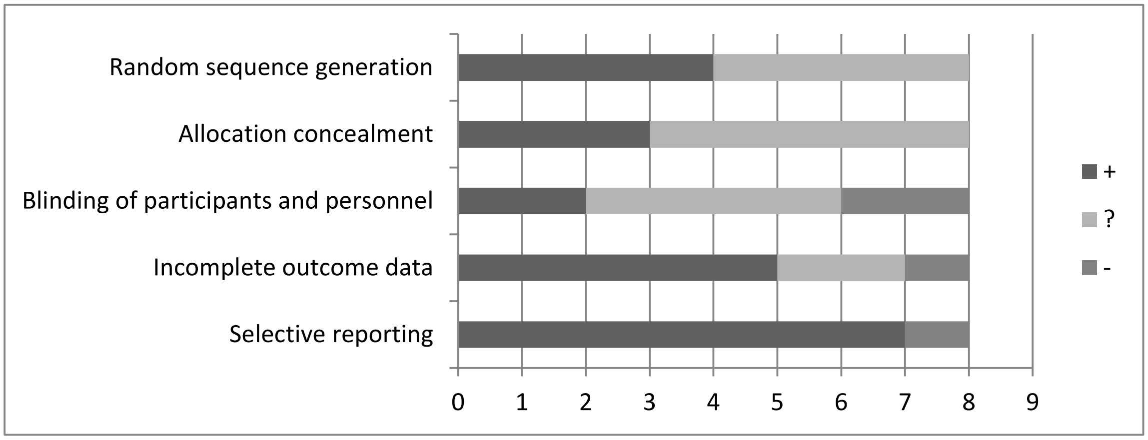
Low dose N-acetylcysteine versus IV saline (CIN outcomes)



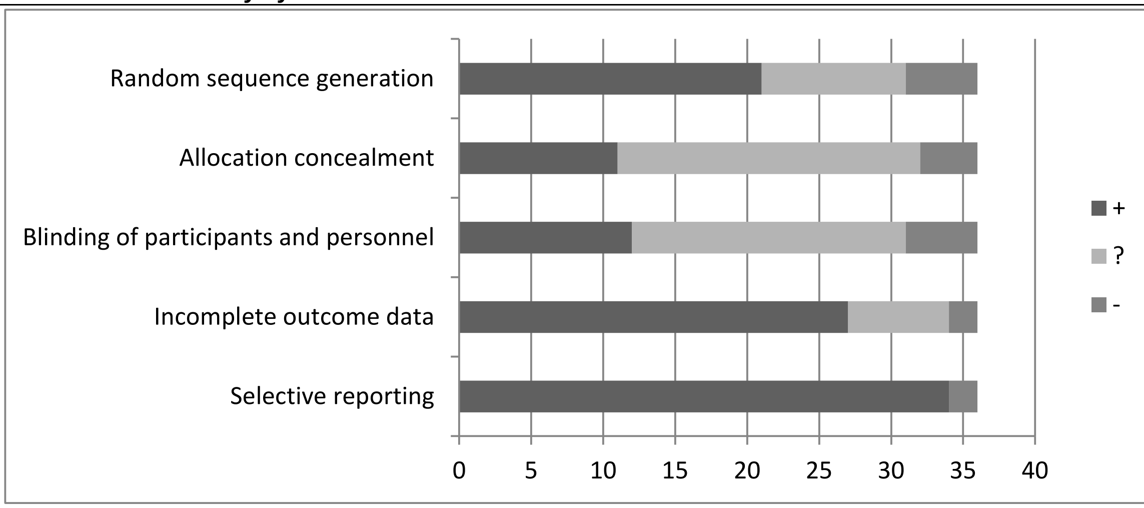
N-acetylcysteine versus intravenous saline: low osmolar contrast media (CIN outcomes)



N-acetylcysteine versus intravenous saline: iso-osmolar contrast media (CIN outcomes)



N-acetylcysteine versus intravenous saline: oral administration of N-acetylcysteine (CIN outcomes)—not shown in the Strength of Evidence Table. Figure does not include information on one study with mixed administration of N-Acetylcysteine



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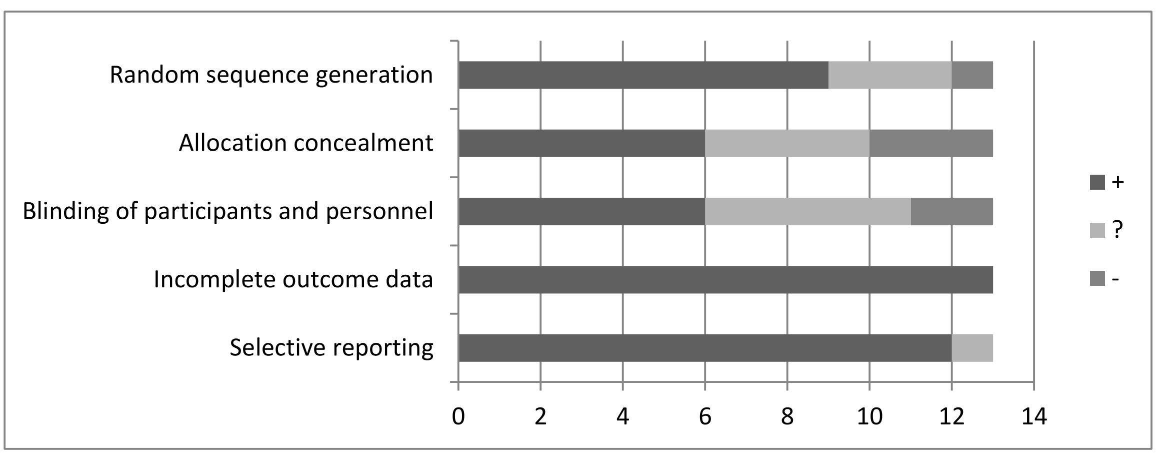
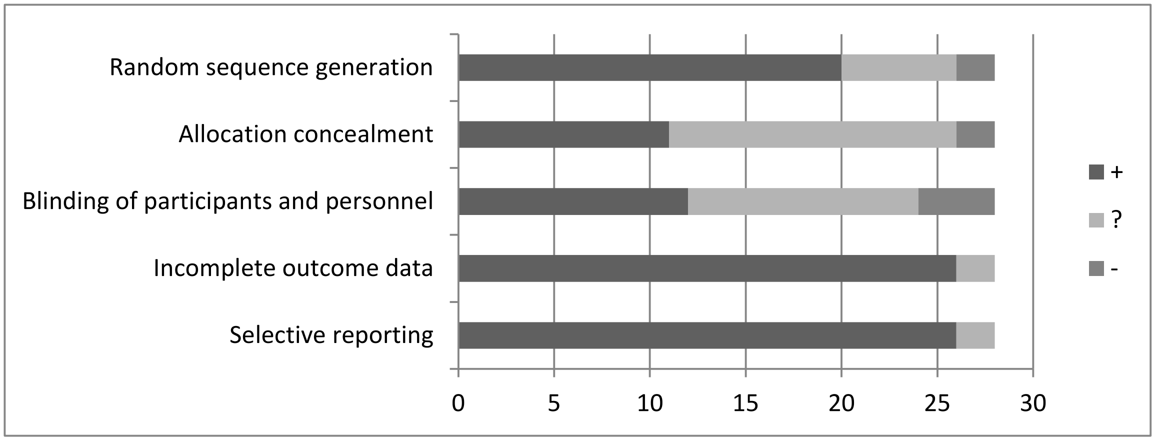
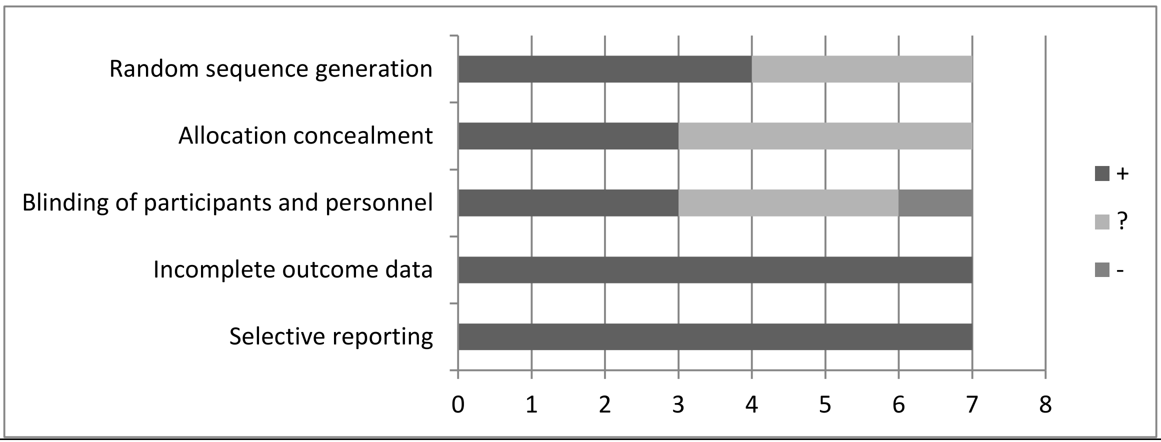


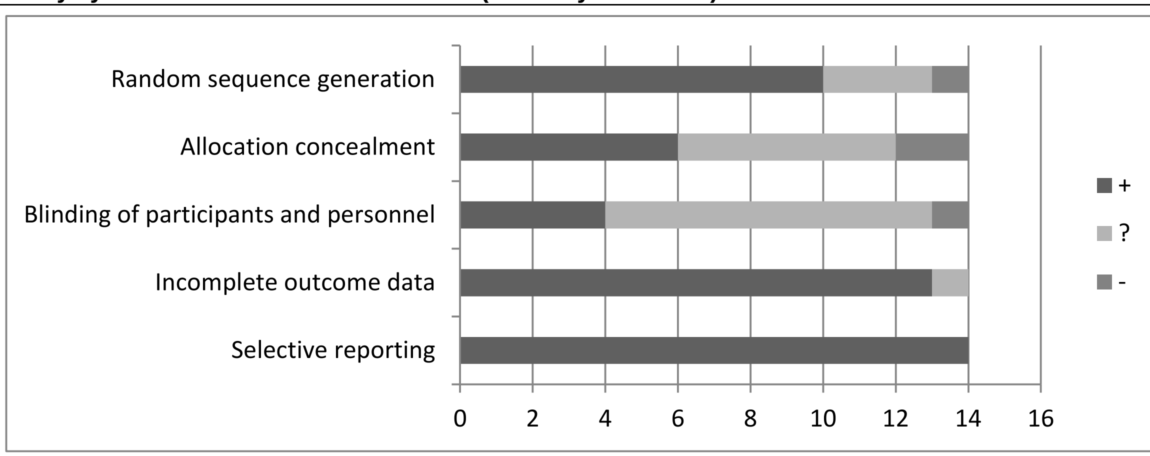
N-acetylcysteine versus intravenous saline (renal replacement therapy outcomes)



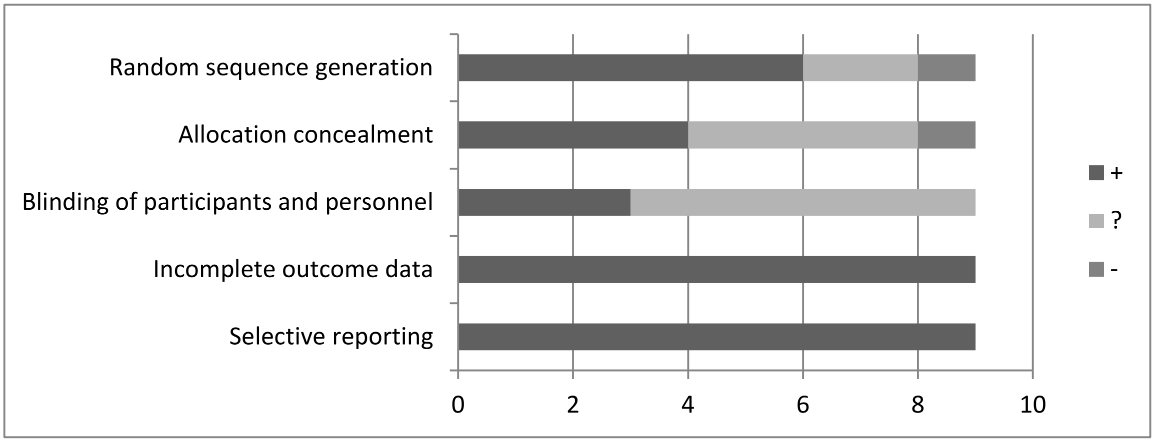
N-acetylcysteine versus intravenous saline (cardiac outcomes)



N-acetylcysteine versus intravenous saline (mortality outcomes)

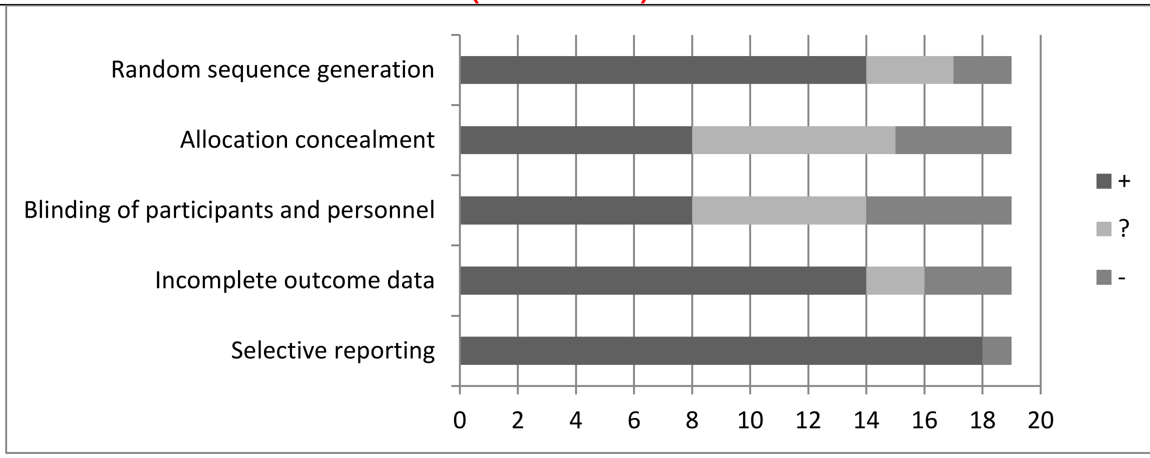


N-acetylcysteine versus intravenous saline (length of stay outcomes)

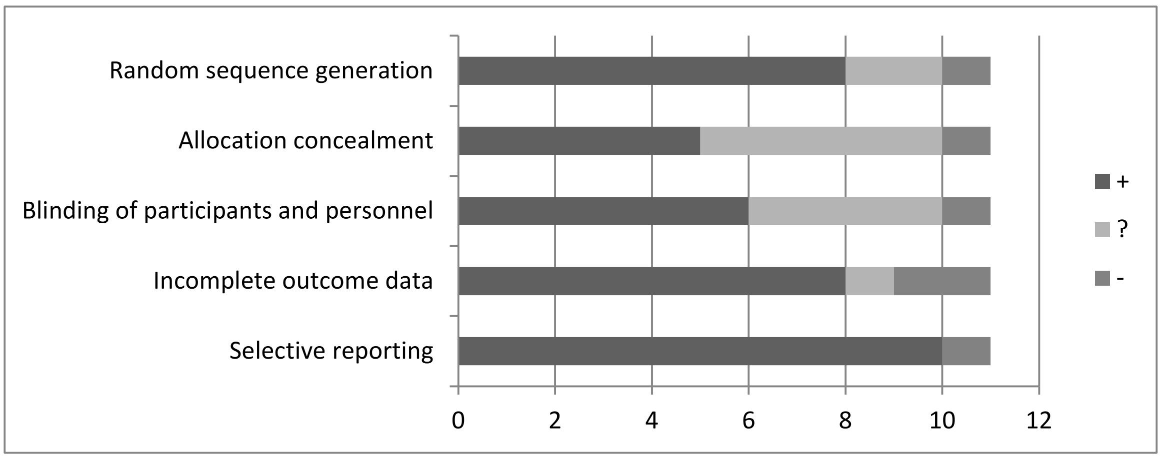


Sodium bicarbonate versus intravenous saline

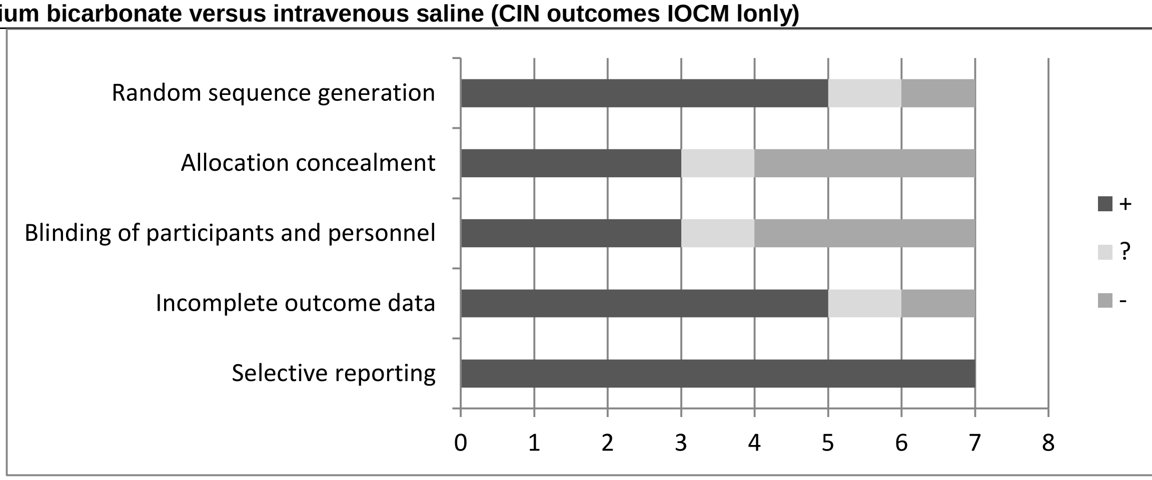
Sodium bicarbonate versus intravenous saline (CIN outcomes)



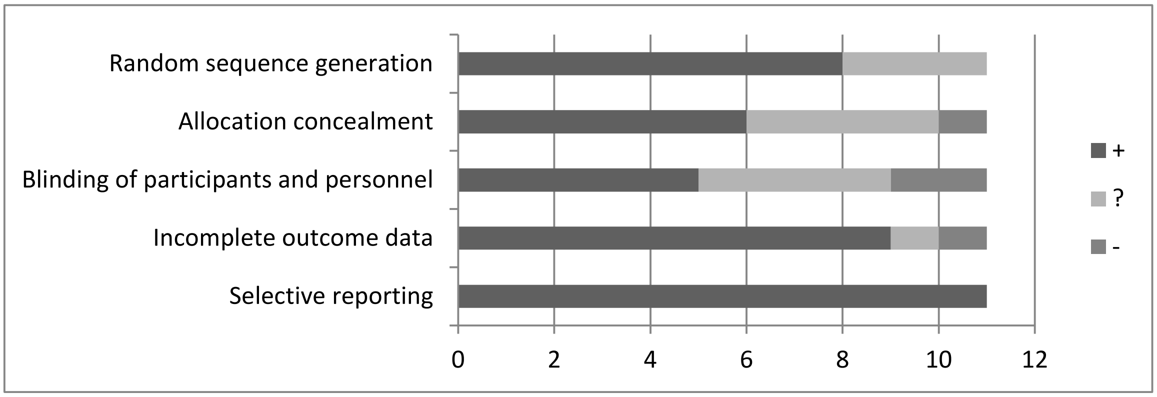
Sodium bicarbonate versus intravenous saline (CIN outcomes LOCM only)



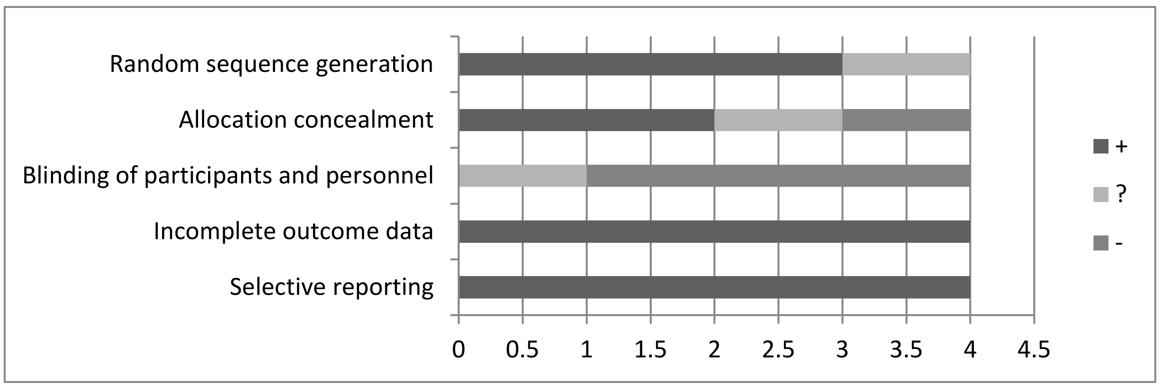
Sodium bicarbonate versus intravenous saline (CIN outcomes IOCM lonly)



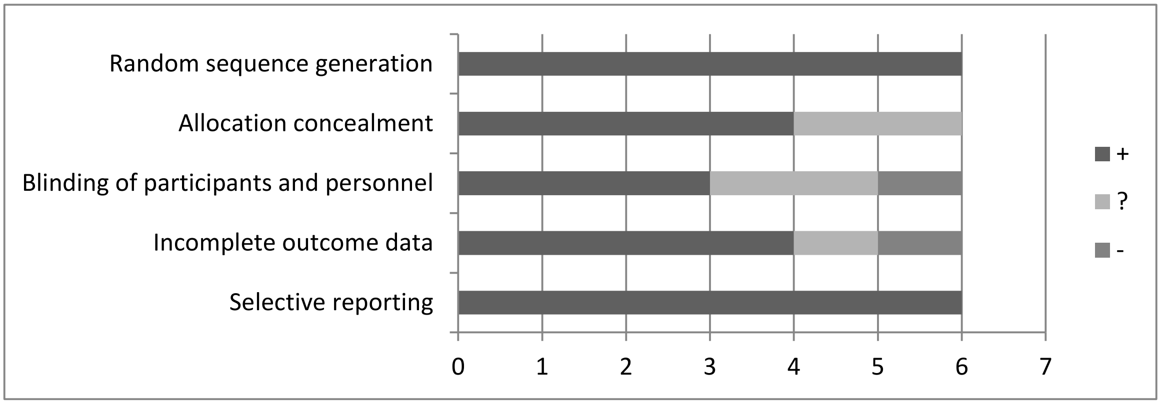
Sodium bicarbonate versus intravenous saline (renal replacement therapy outcomes)



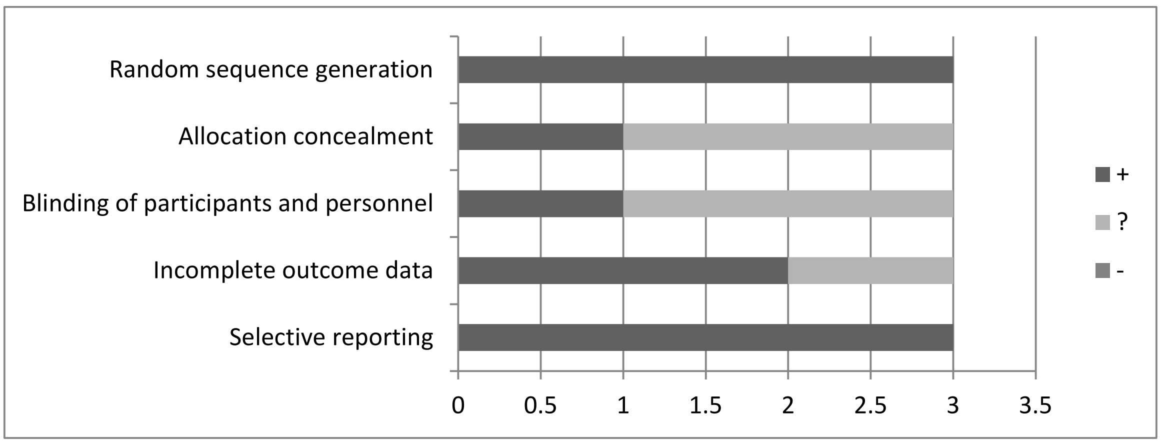
Sodium bicarbonate versus intravenous saline (cardiac outcomes)



Sodium bicarbonate versus intravenous saline (mortality outcomes)

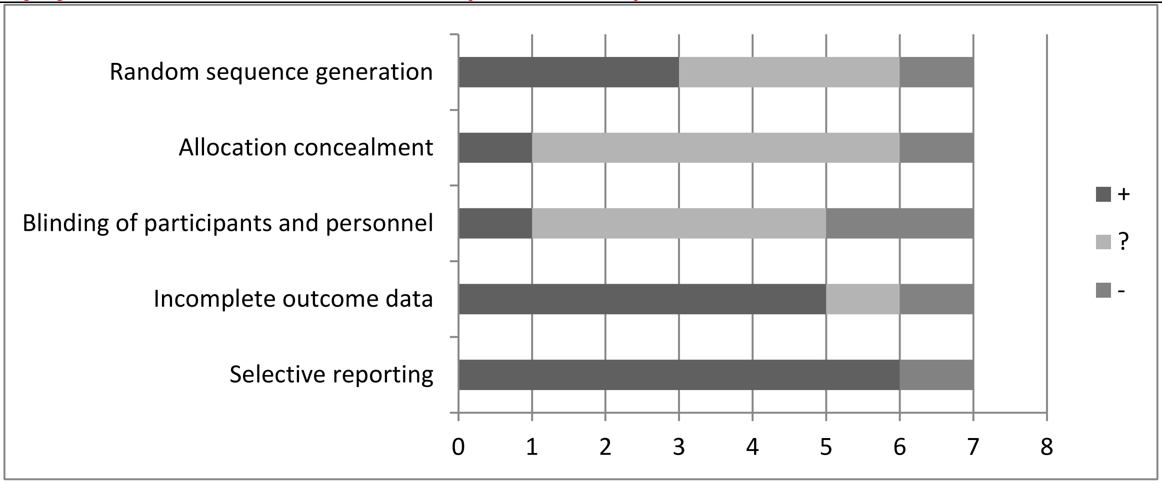


Sodium bicarbonate versus intravenous saline (length of stay outcomes)

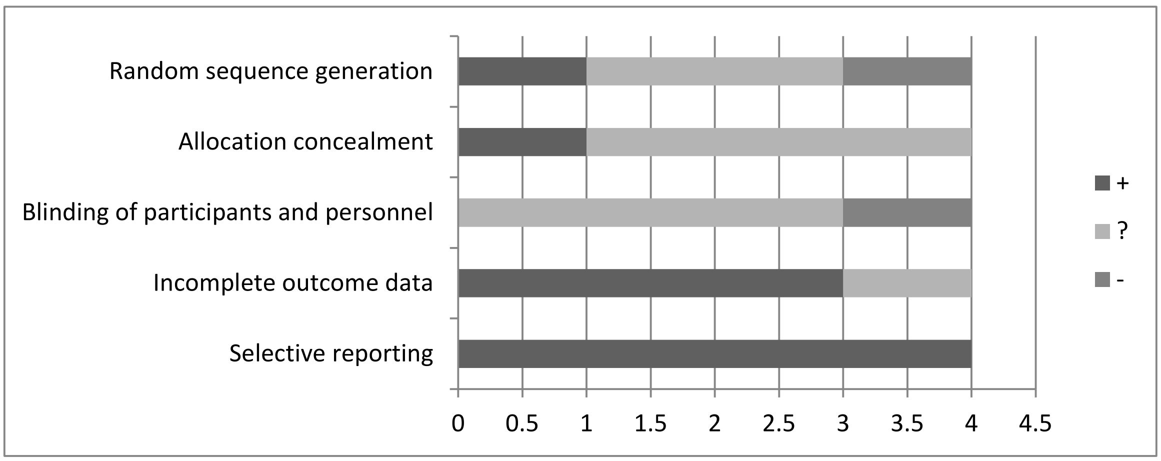


N-acetylcysteine versus sodium bicarbonate

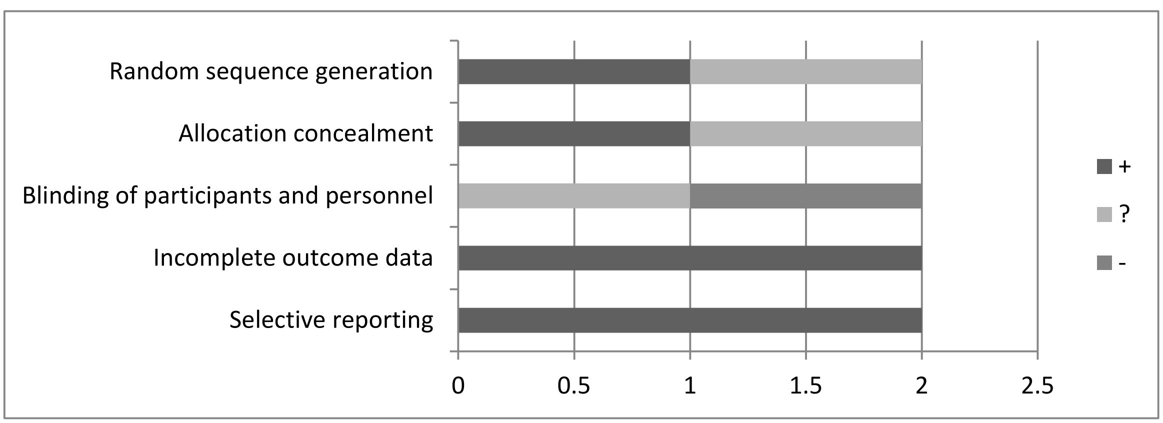
N-acetylcysteine versus sodium bicarbonate (CIN outcomes)



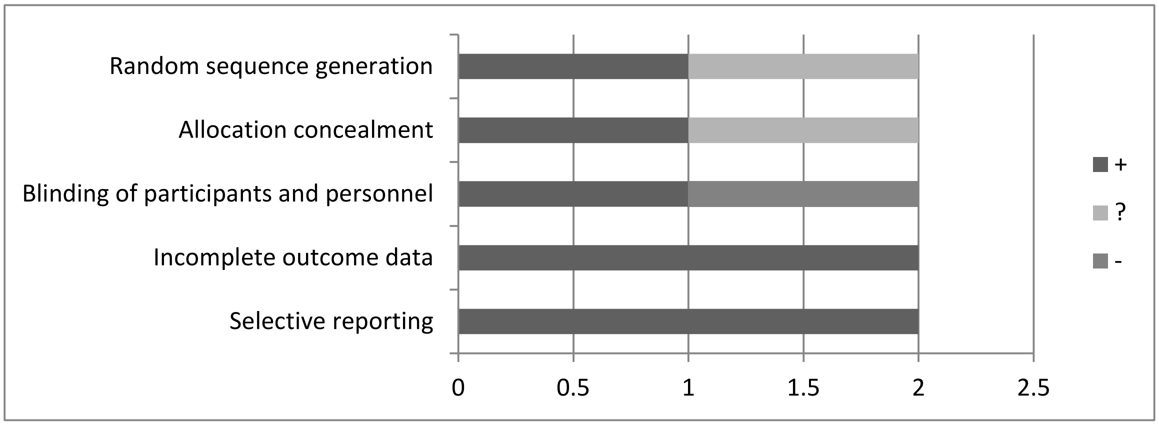
N-acetylcysteine versus sodium bicarbonate (renal replacement therapy outcomes)



N-acetylcysteine versus sodium bicarbonate (cardiac outcomes)

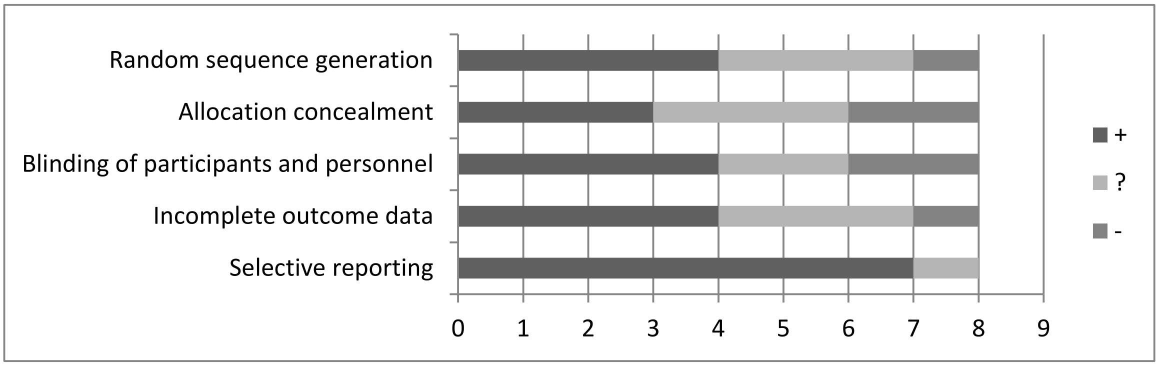


N-acetylcysteine versus sodium bicarbonate (mortality outcomes)

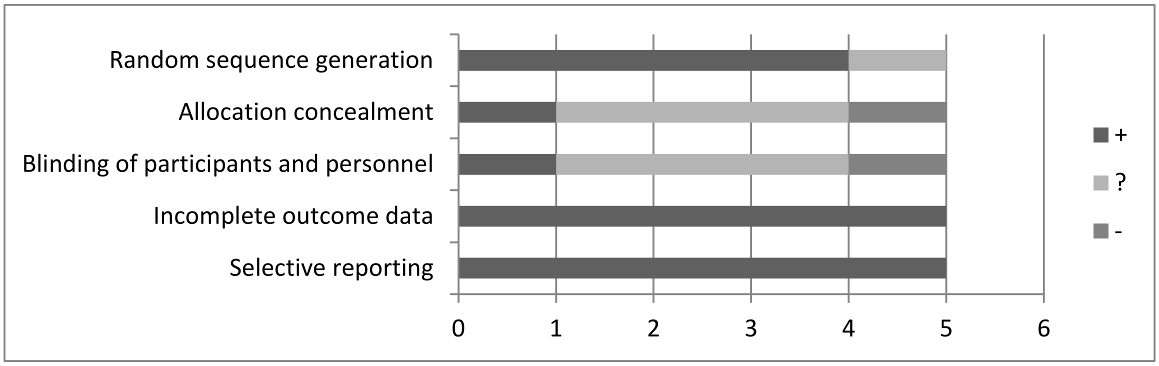


Statin versus intravenous saline or statin plus N-acetylcysteine versus N-acetylcysteine alone

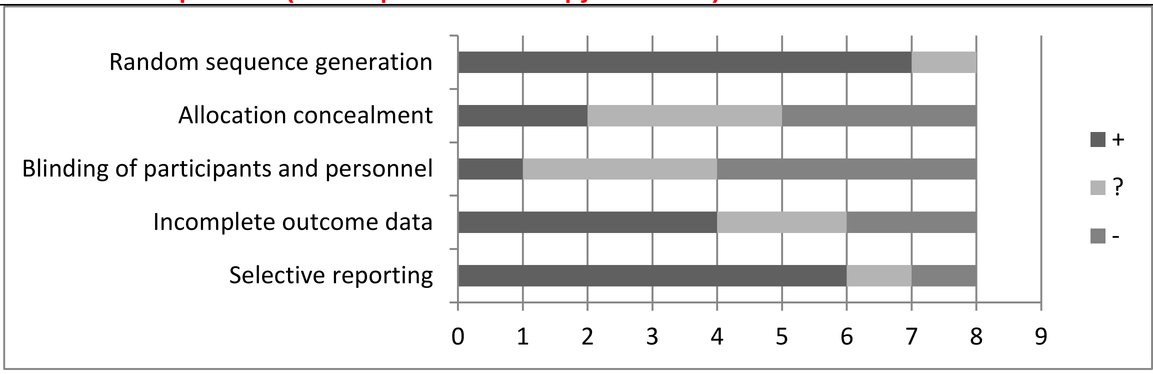
Statin versus intravenous saline (CIN outcomes)



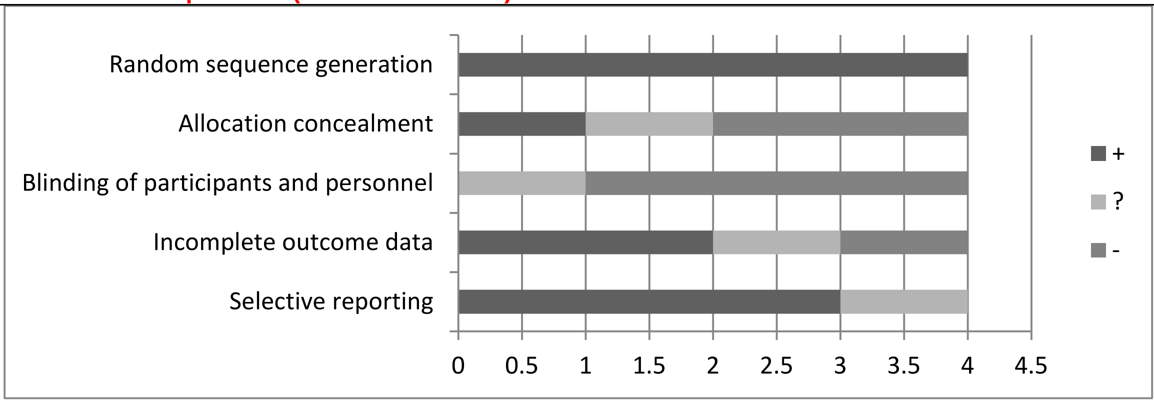
Statin plus N-acetylcysteine versus N-acetylcysteine (CIN outcomes)



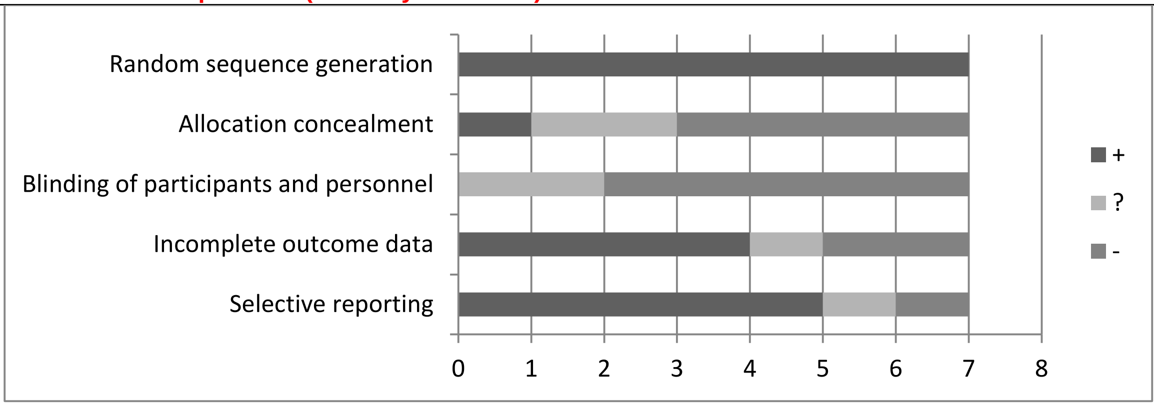
Statin versus all comparisons (renal replacement therapy outcomes)



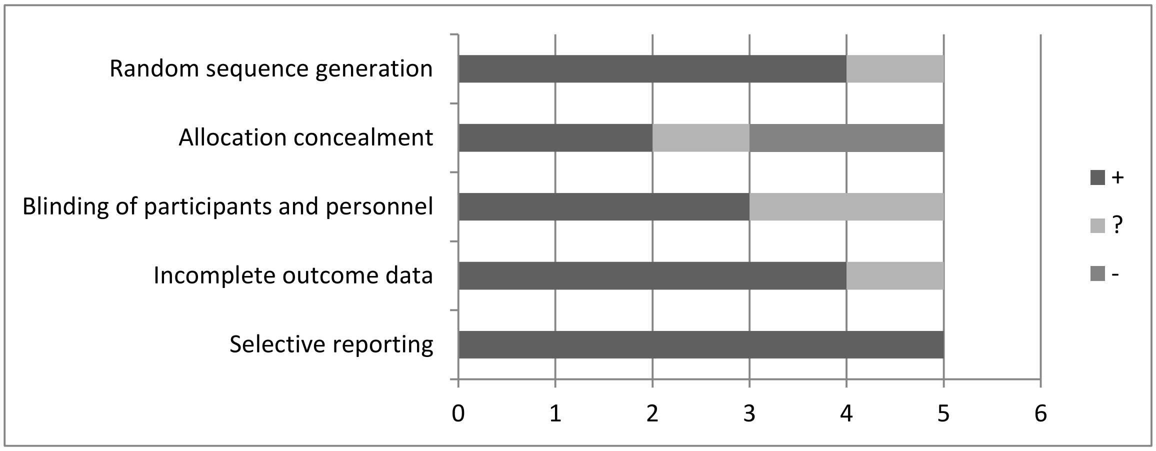
Statin versus all comparisons (cardiac outcomes)



Statin versus all comparisons (mortality outcomes)

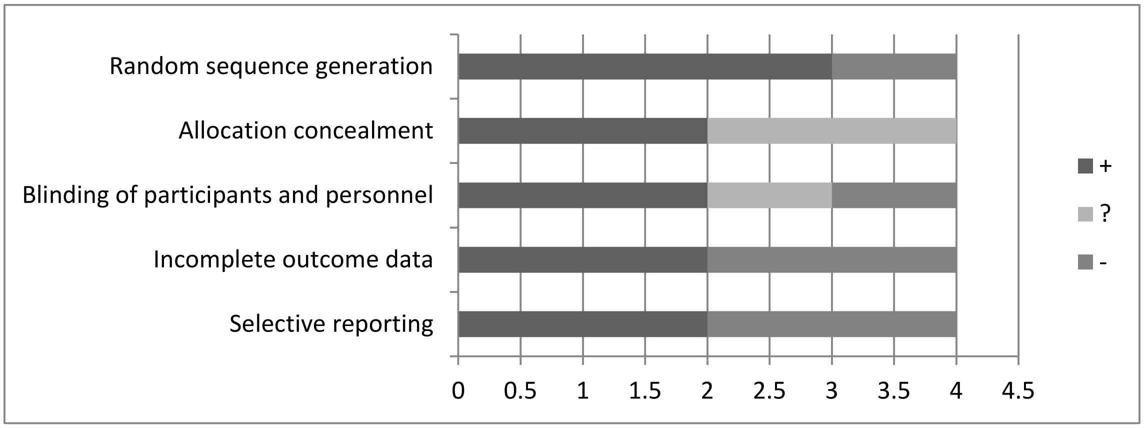


Statin versus all comparisons (length of stay outcomes)

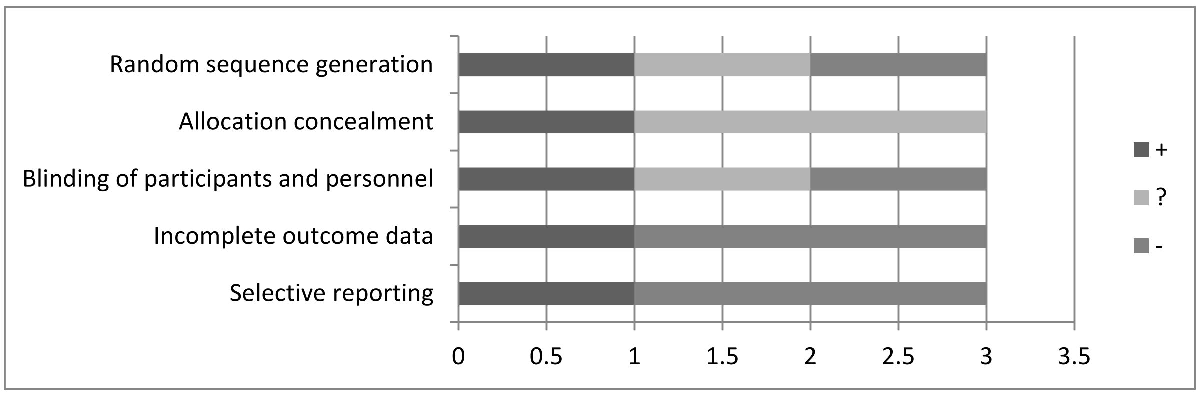


Adenosine versus intravenous saline

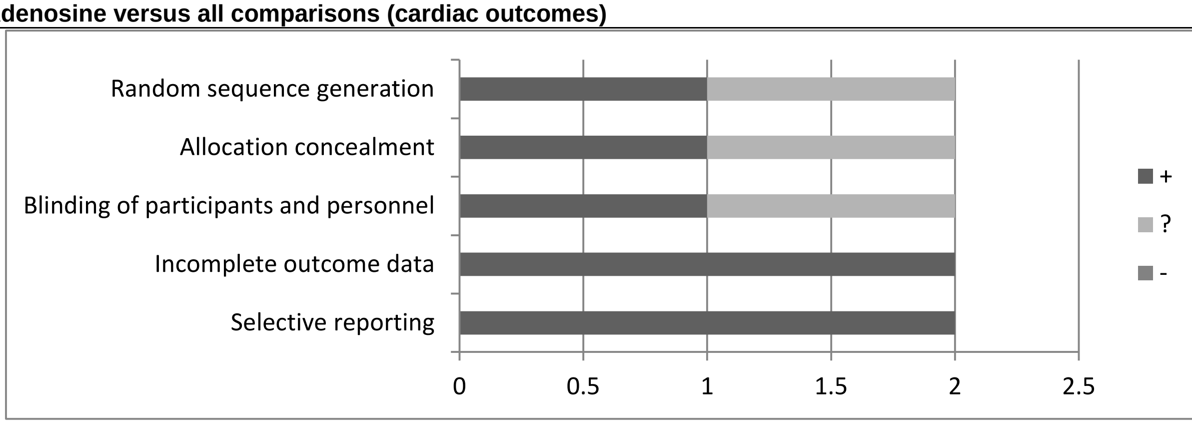
Adenosine versus all comparisons (CIN outcomes)



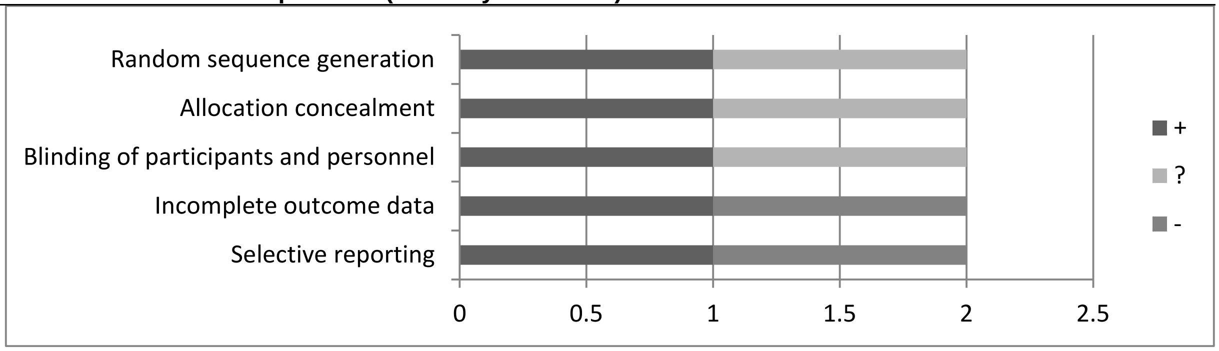
Adenosine versus all comparisons (renal replacement therapy outcomes)



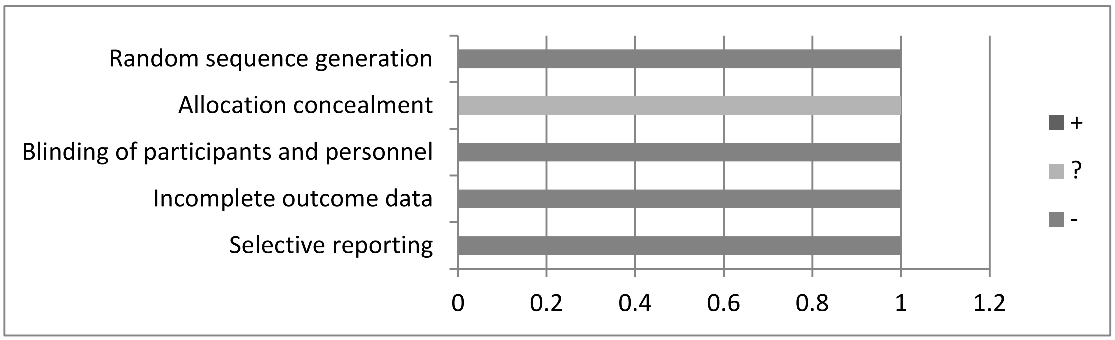
Adenosine versus all comparisons (cardiac outcomes)



Adenosine versus all comparisons (mortality outcomes)

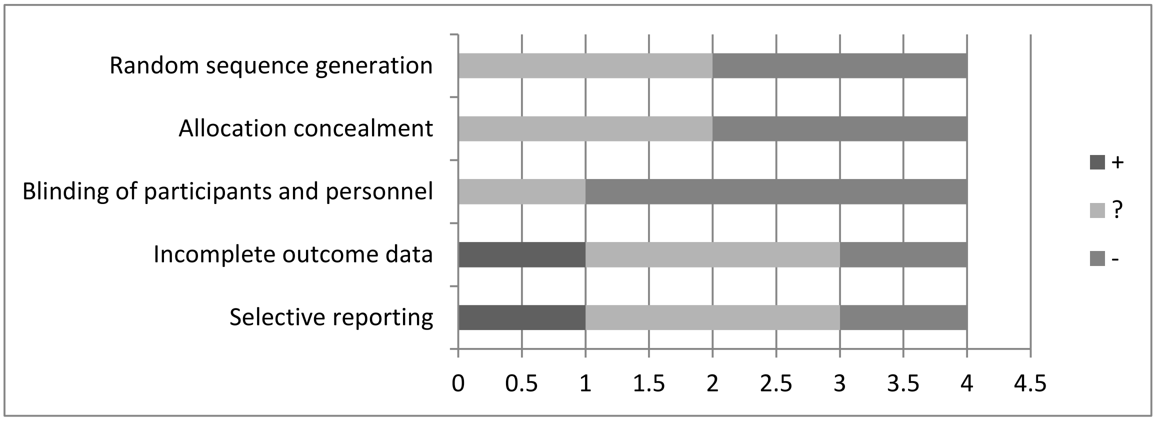


Adenosine versus all comparisons (length of stay outcomes)

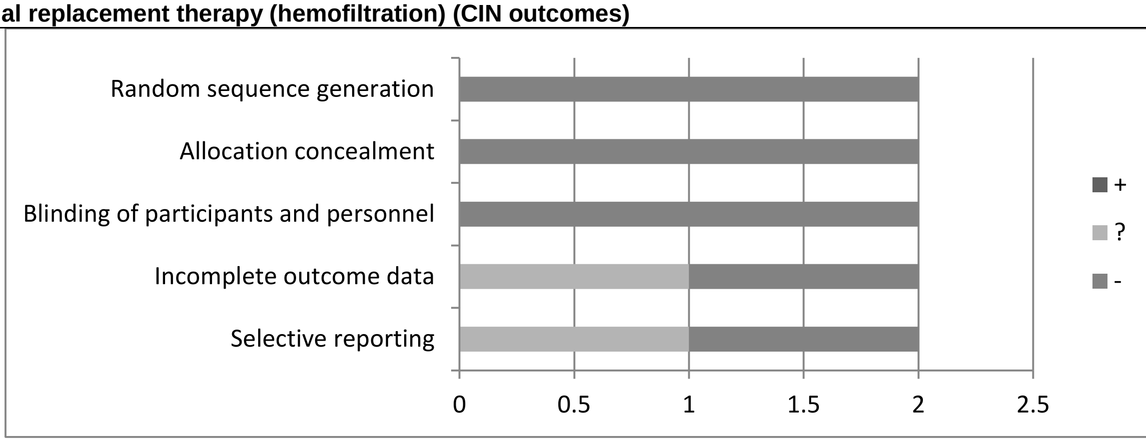


Renal replacement therapy

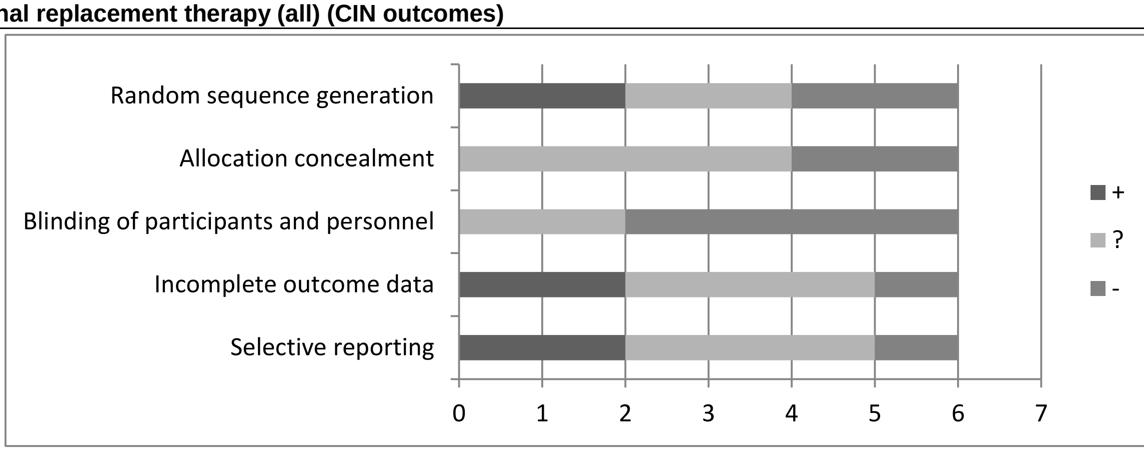
Renal replacement therapy (hemodialysis) (CIN outcomes)



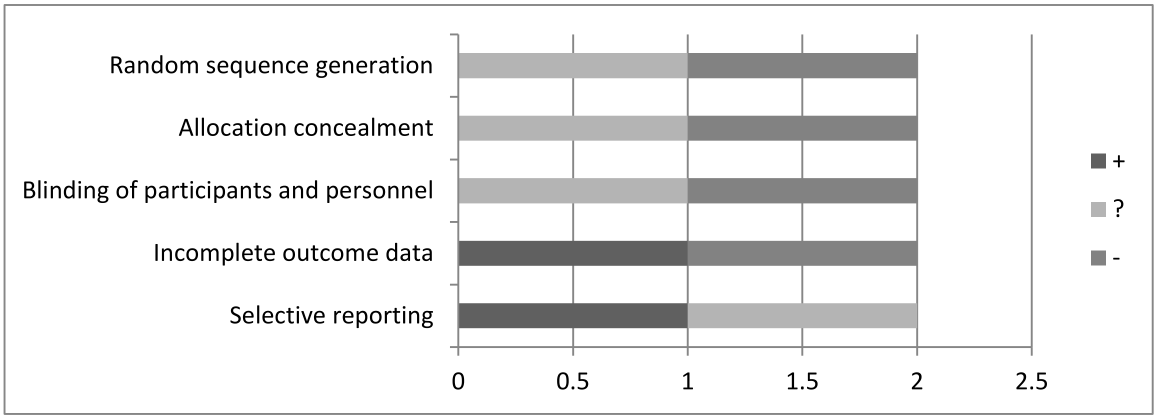
Renal replacement therapy (hemofiltration) (CIN outcomes)



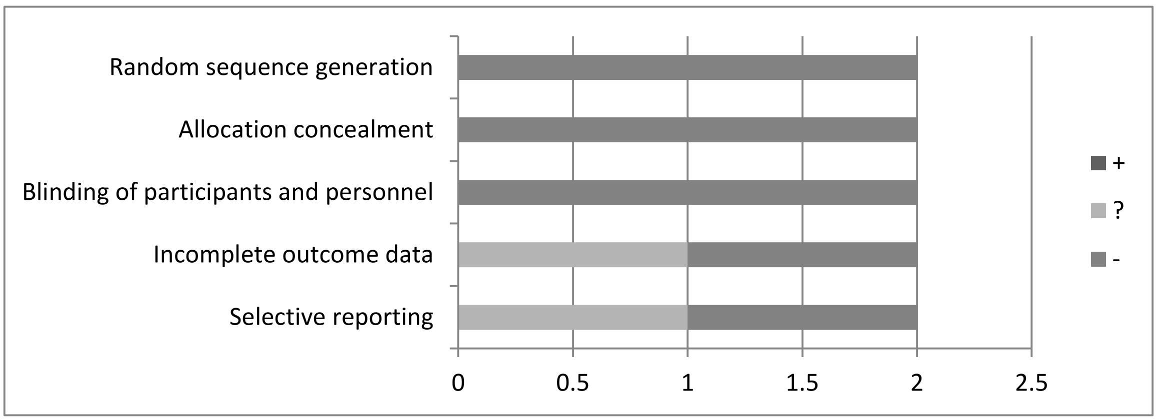
Renal replacement therapy (all) (CIN outcomes)



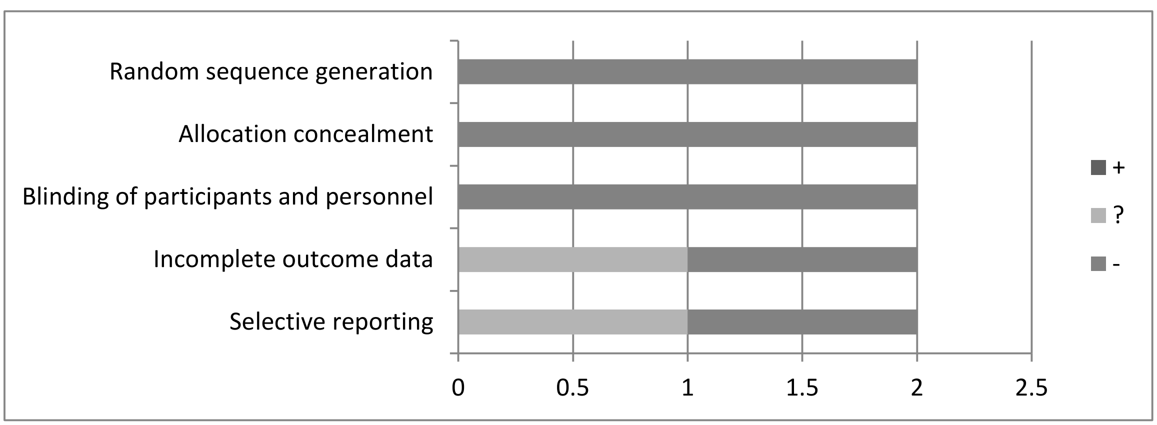
Renal replacement therapy (hemodialysis) (renal replacement therapy outcomes)



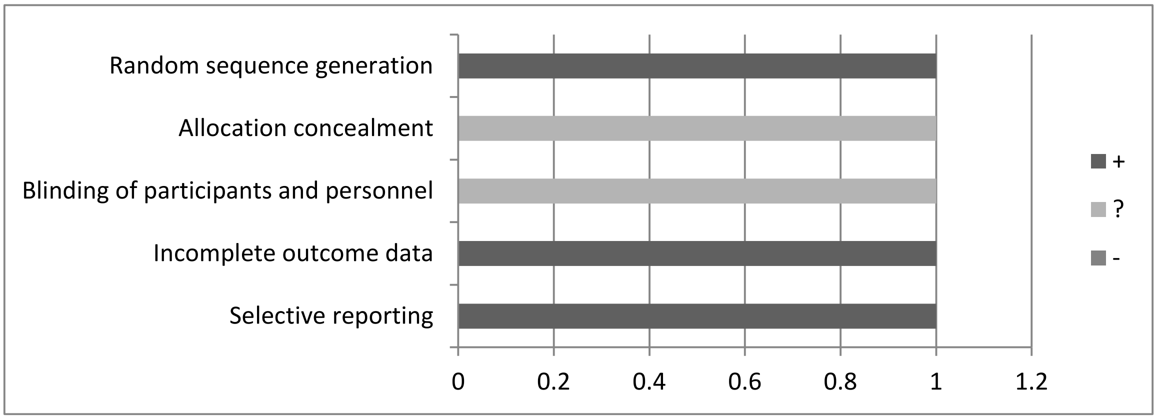
Renal replacement therapy (hemofiltration) (renal replacement therapy outcomes)



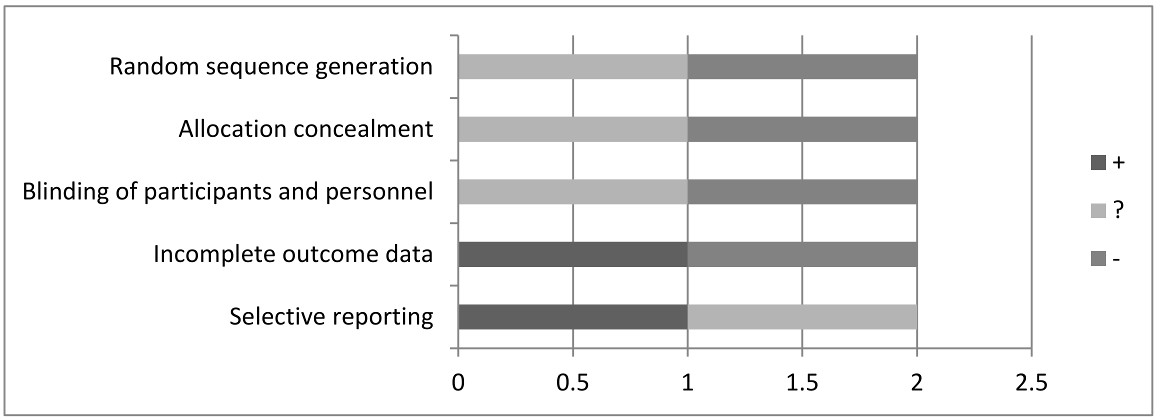
Renal replacement therapy (hemodialysis) (cardiac outcomes)



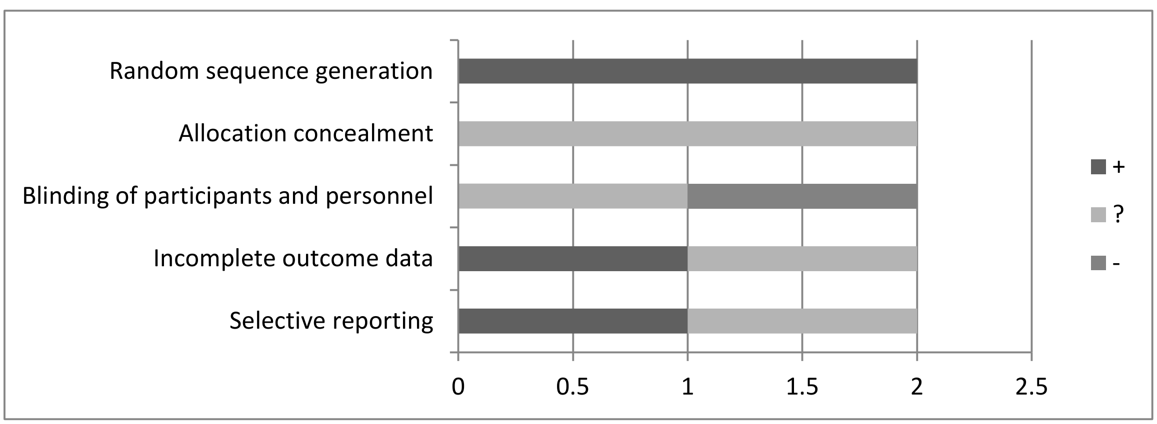
Renal replacement therapy (hemofiltration) (cardiac outcomes)



Renal replacement therapy (hemodialysis) (mortality outcomes)

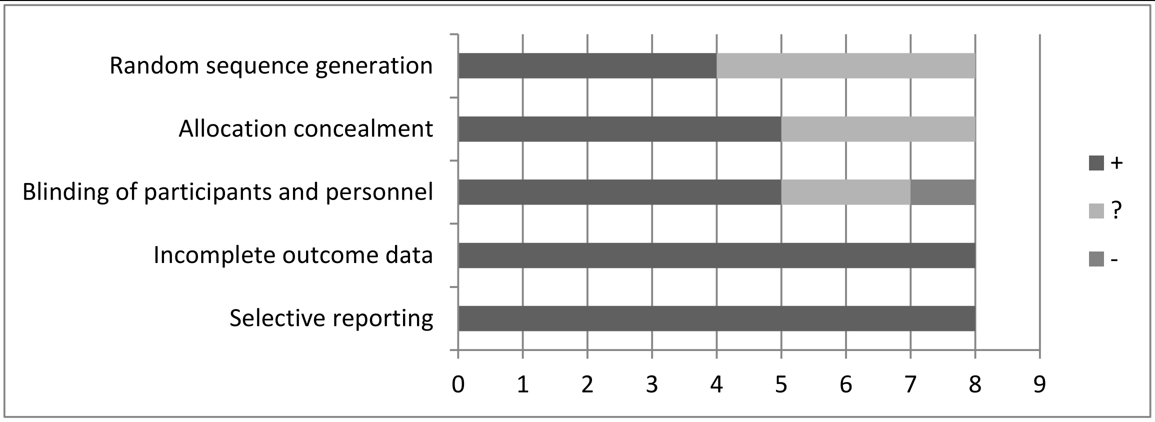


Renal replacement therapy (hemofiltration) (mortality outcomes)

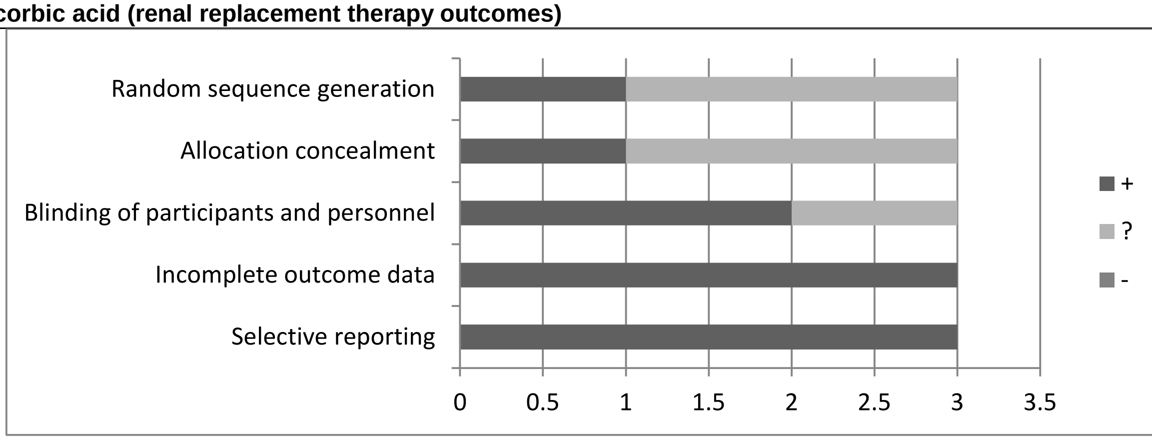


Ascorbic acid

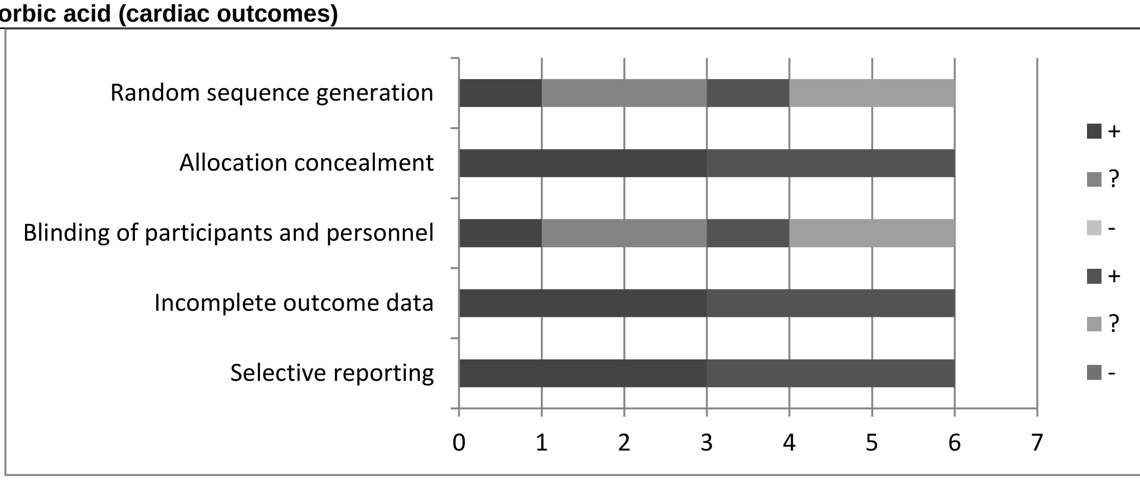
Ascorbic acid (CIN outcomes)



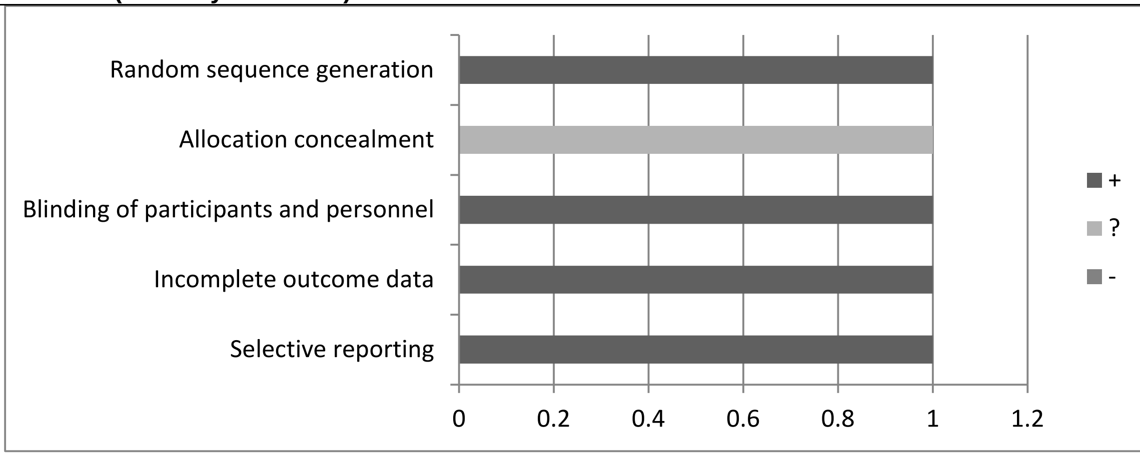
Ascorbic acid (renal replacement therapy outcomes)



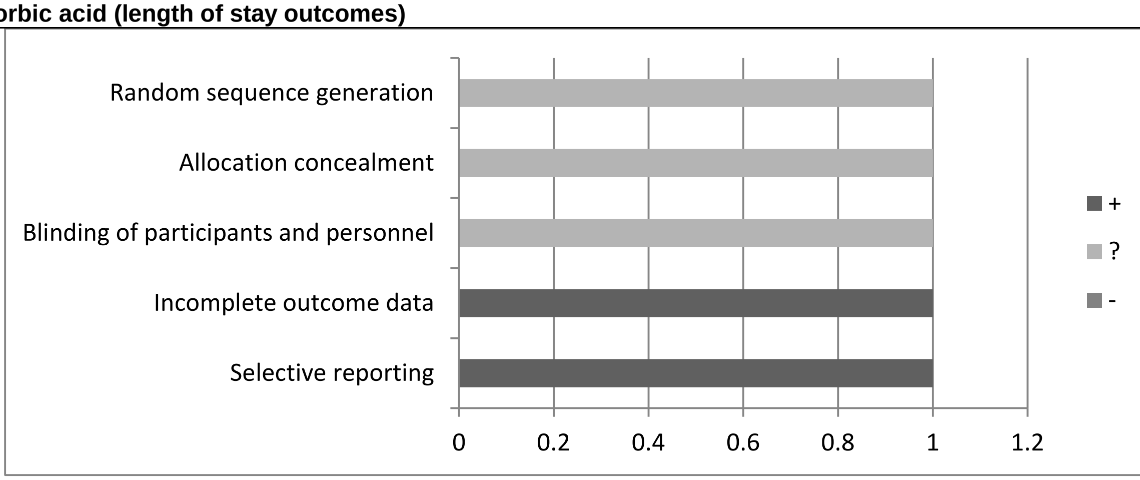
Ascorbic acid (cardiac outcomes)



Ascorbic acid (mortality outcomes)

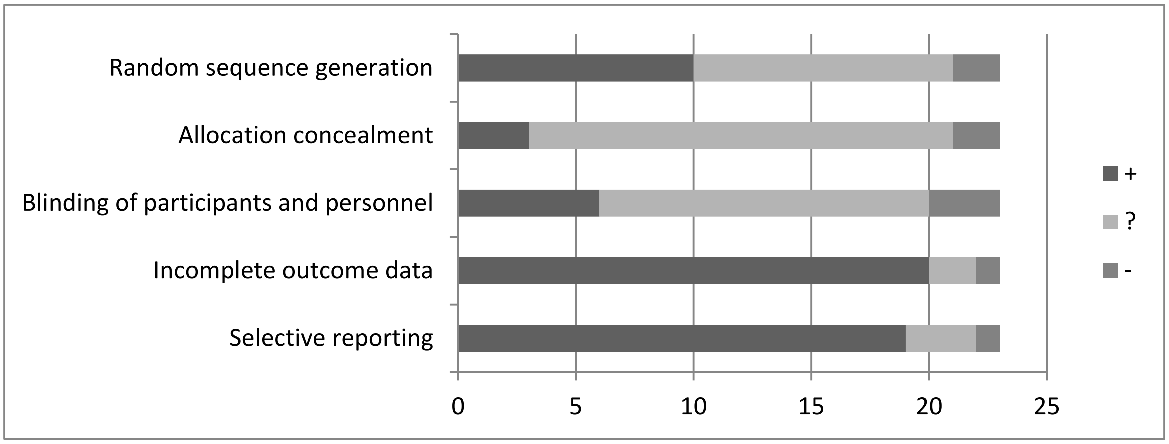


Ascorbic acid (length of stay outcomes)

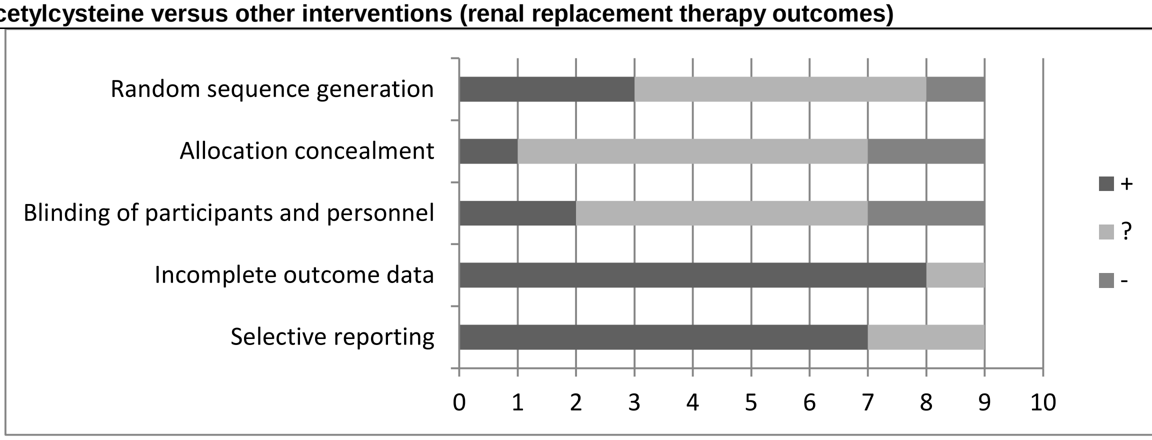


N-acetylcysteine versus other interventions

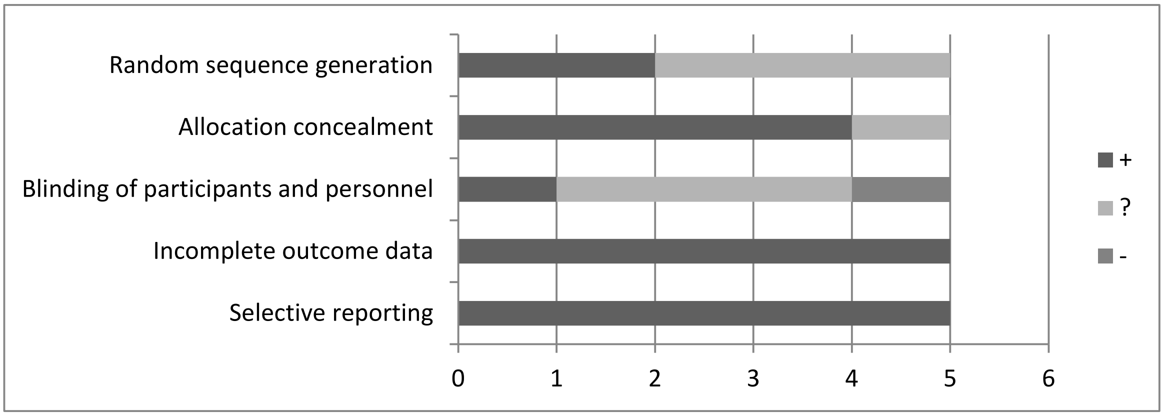
N-acetylcysteine versus other interventions (CIN outcomes)



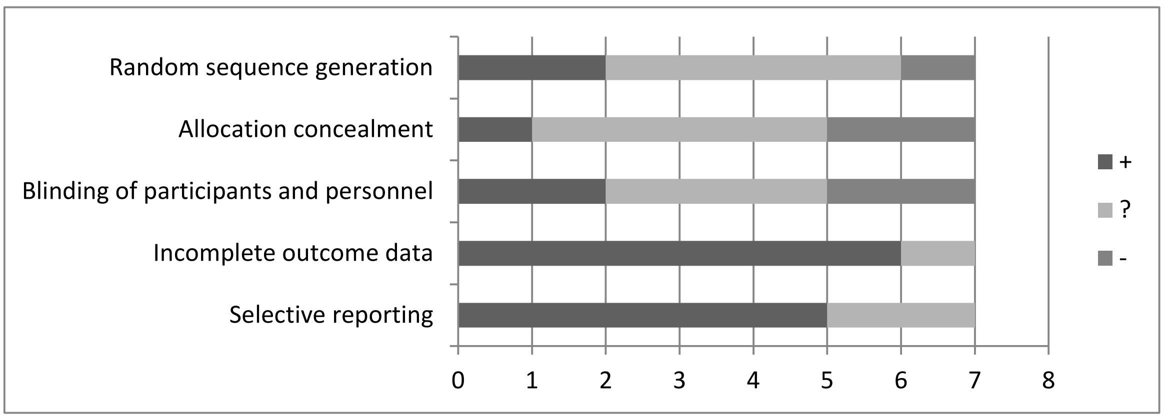
N-acetylcysteine versus other interventions (renal replacement therapy outcomes)



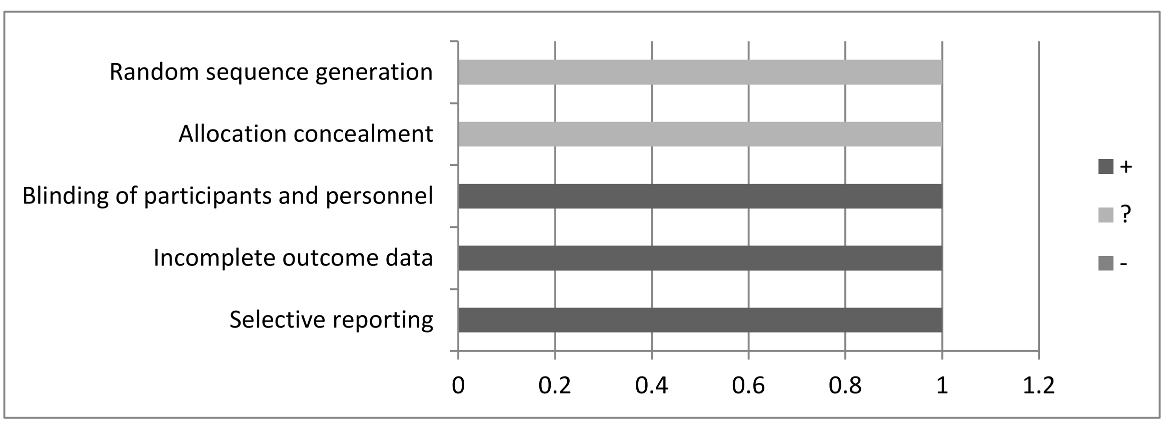
N-acetylcysteine versus other interventions (cardiac outcomes)



N-acetylcysteine versus other interventions (mortality outcomes)

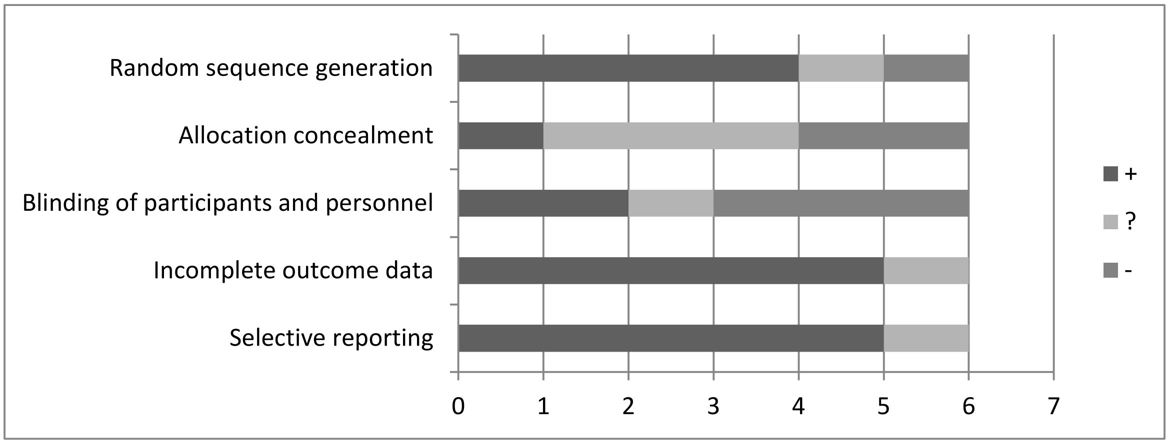


N-acetylcysteine versus other interventions (length of stay outcomes)

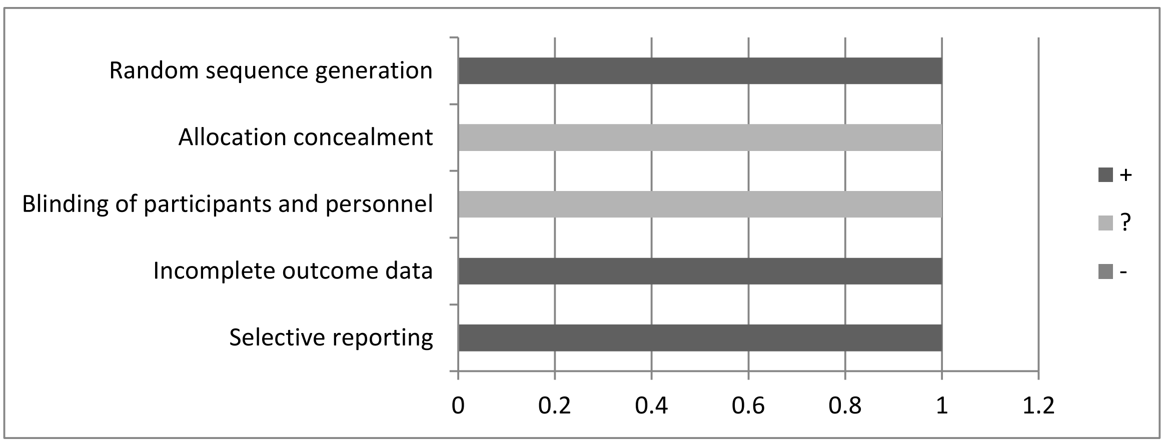


Sodium bicarbonate versus other interventions

Sodium bicarbonate versus other interventions (CIN outcomes)

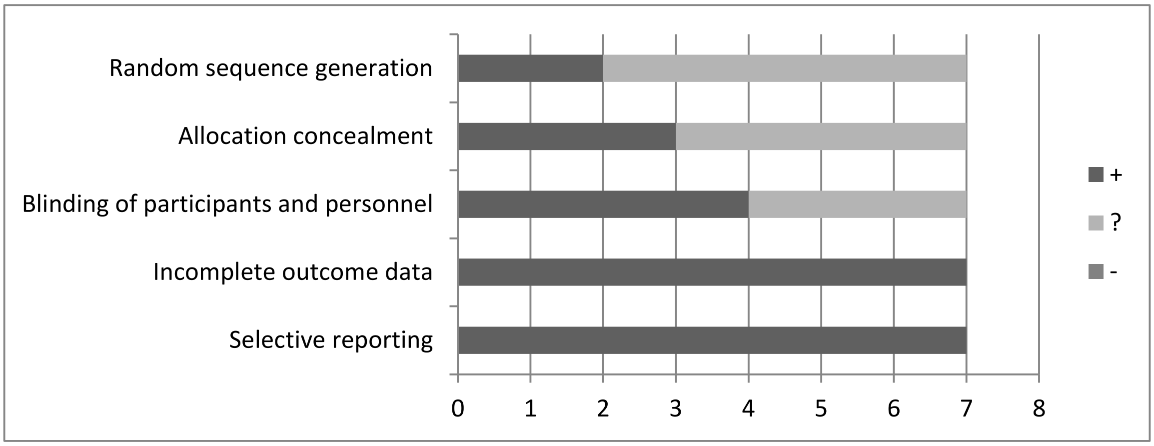


Sodium bicarbonate versus other interventions (length of stay outcomes)

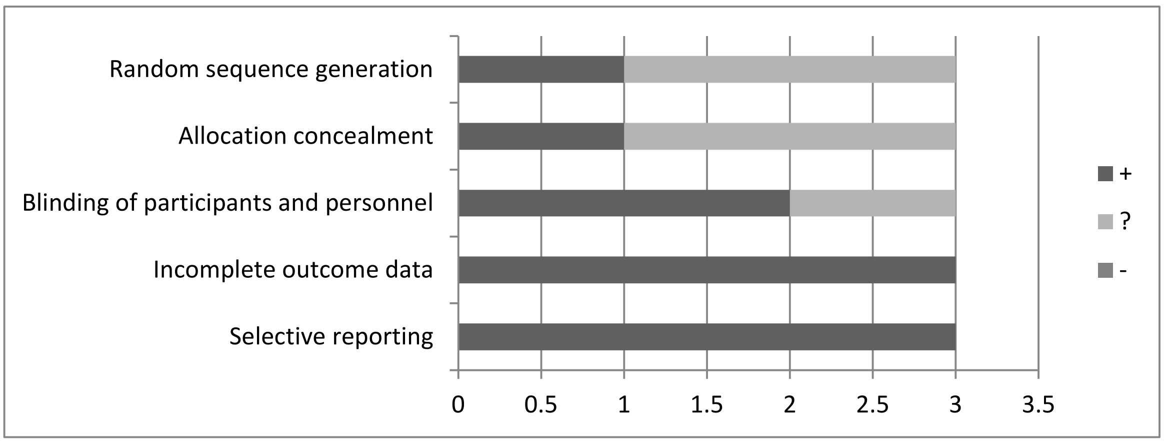


N-acetylcysteine plus sodium bicarbonate versus other interventions

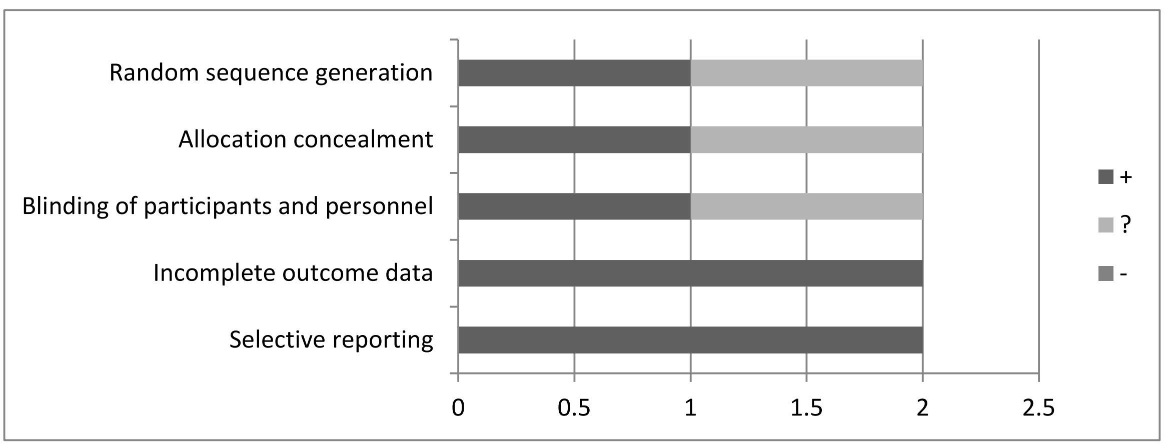
N-acetylcysteine plus sodium bicarbonate versus other interventions (CIN outcomes)



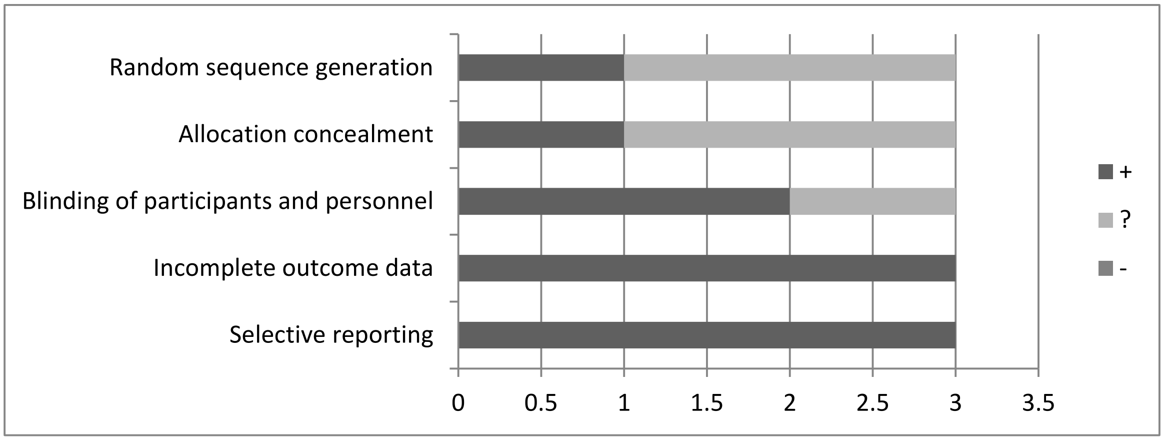
N-acetylcysteine plus sodium bicarbonate versus other interventions (renal replacement therapy outcomes)



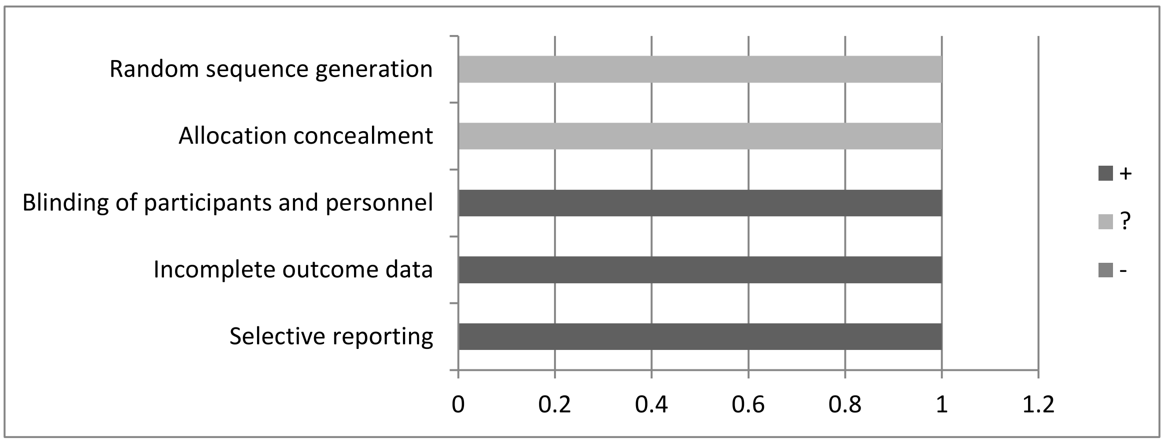
N-acetylcysteine plus sodium bicarbonate versus other interventions (cardiac outcomes)



N-acetylcysteine plus sodium bicarbonate versus other interventions (mortality outcomes)

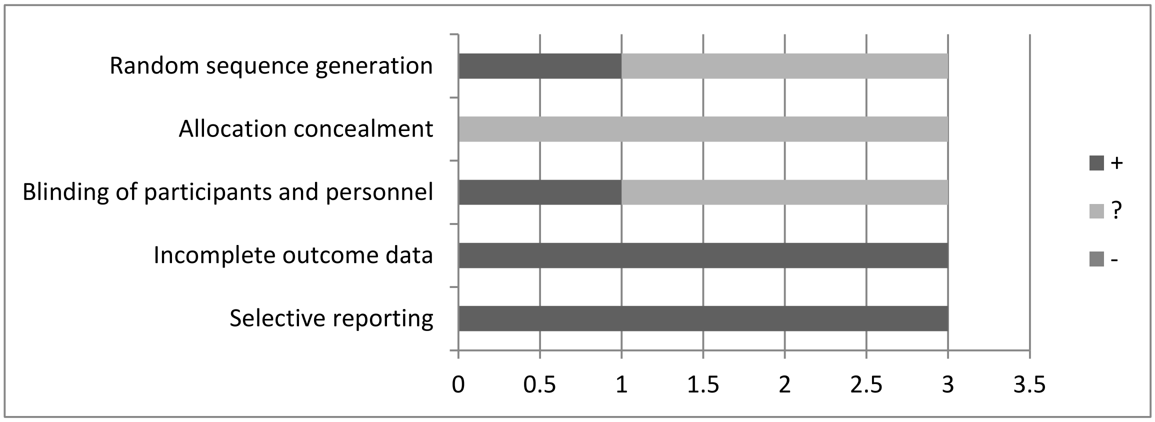


N-acetylcysteine plus sodium bicarbonate versus other interventions (length of stay outcomes)

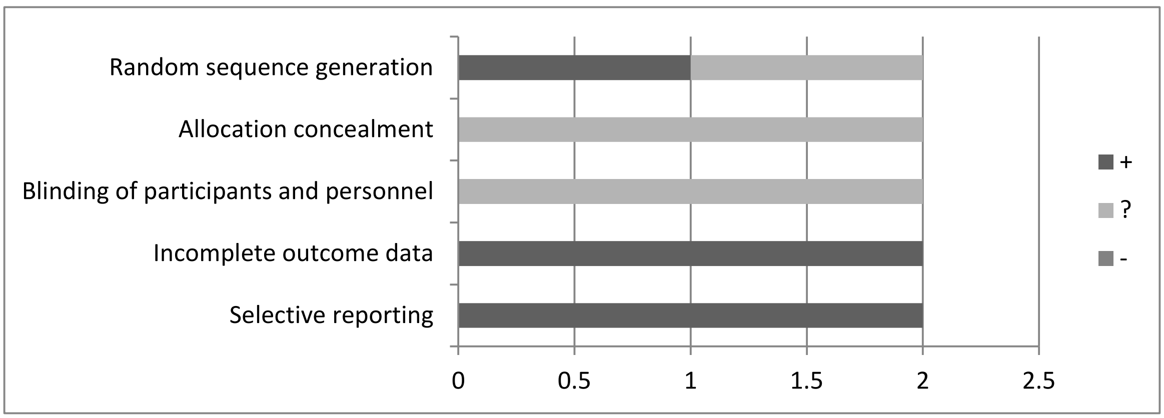


Diuretics

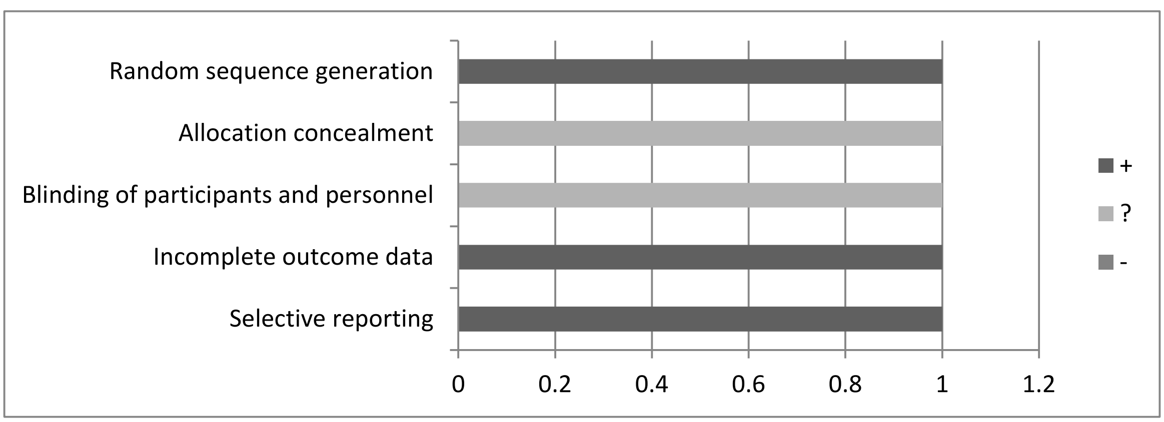
Diuretics (CIN outcomes)



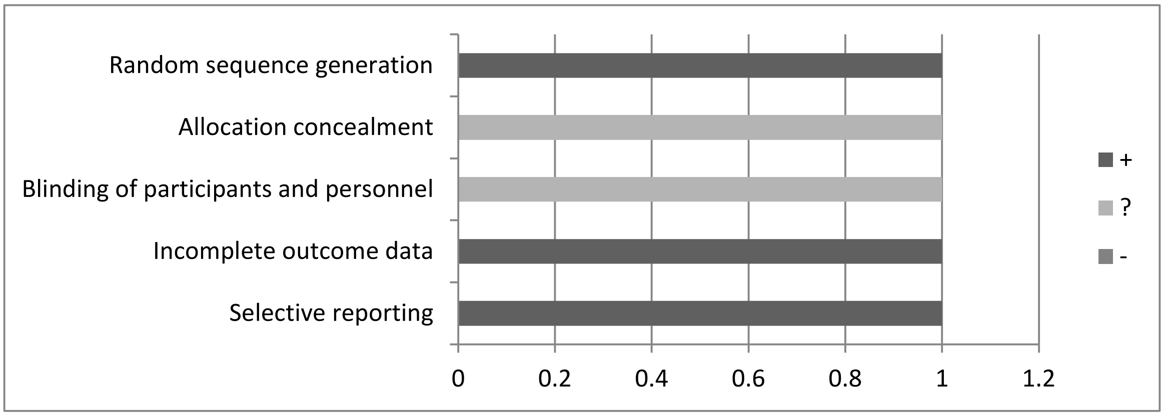
Diuretics (renal replacement outcomes)



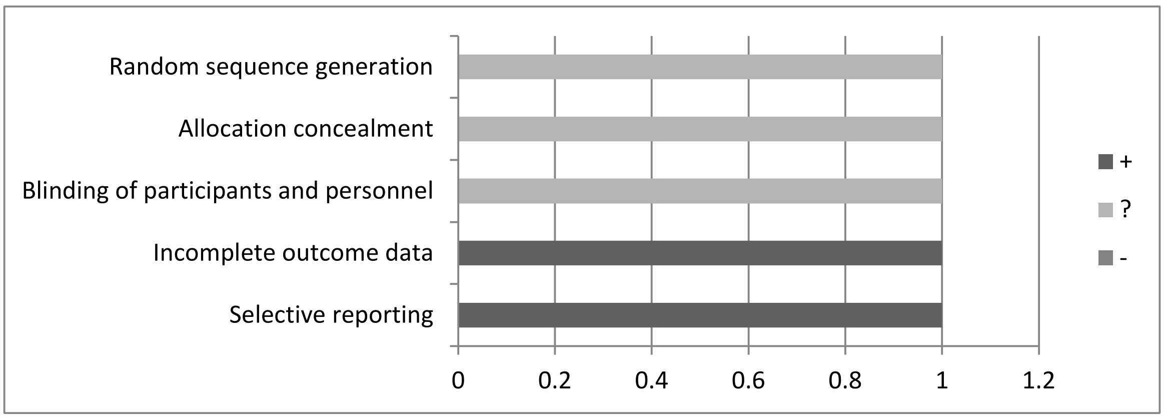
Diuretics (cardiac outcomes)



Diuretics (mortality outcomes)

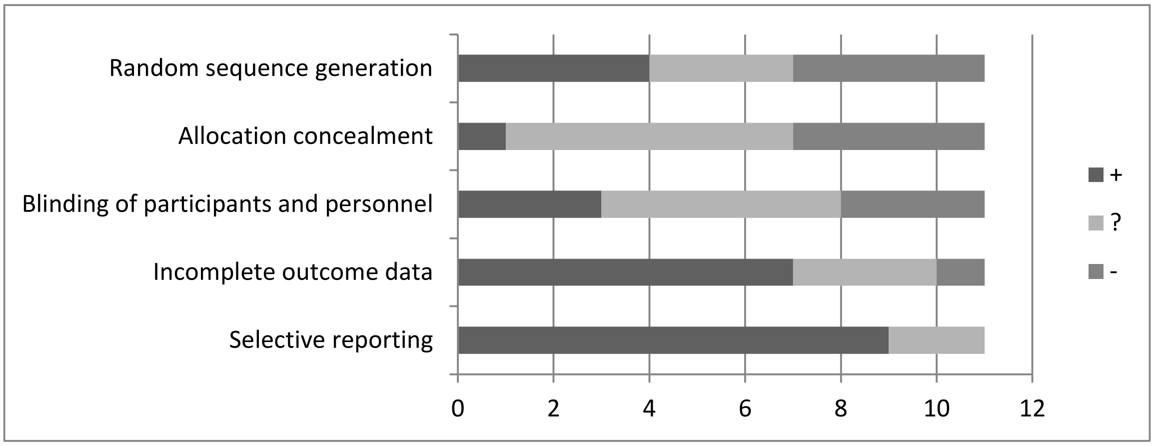


Diuretics (length of stay outcomes)

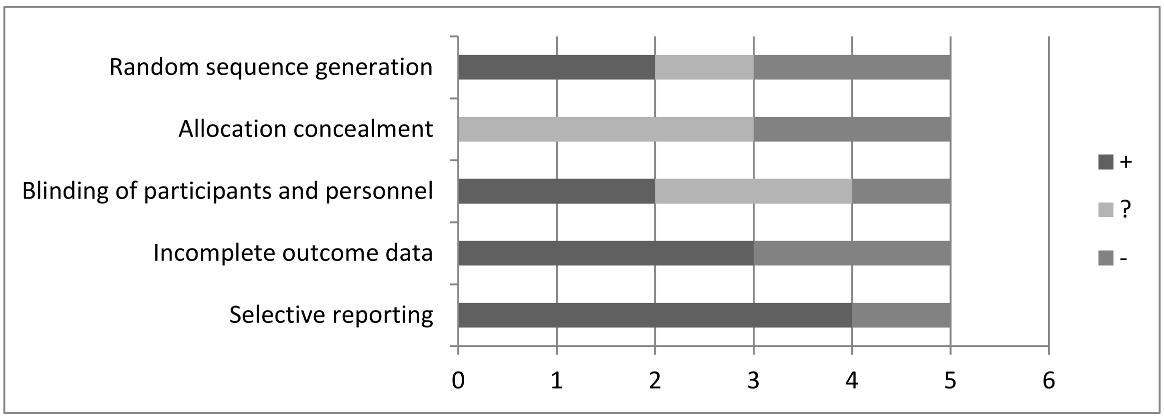


Vasoactive agents

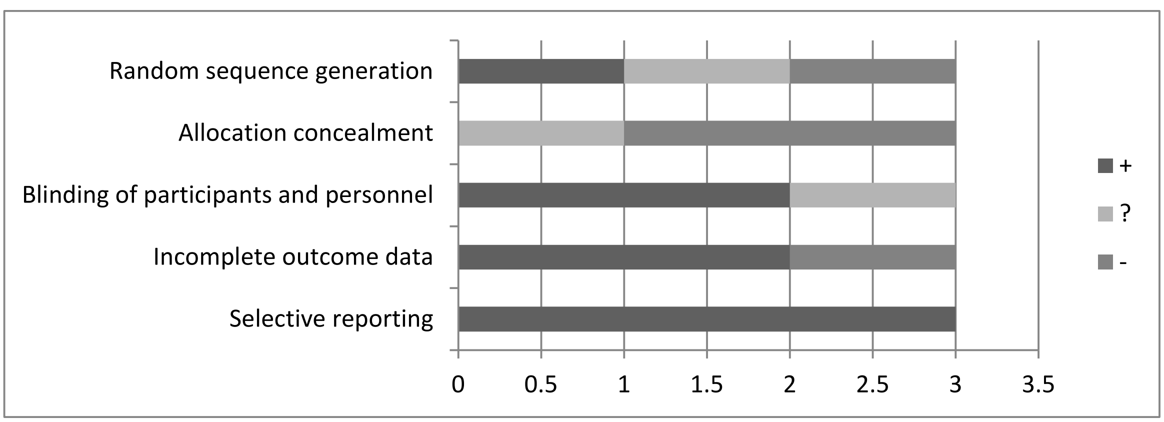
Vasoactive agents (CIN outcomes)



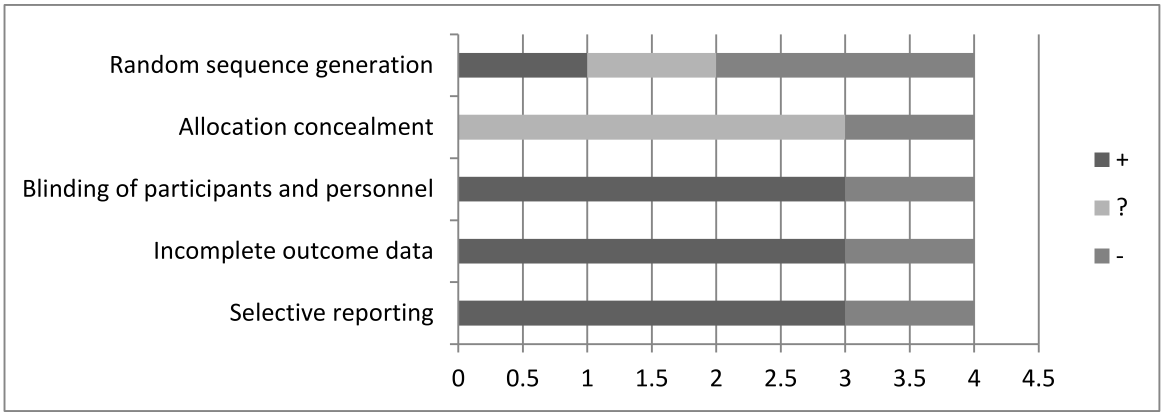
Vasoactive agents (renal replacement therapy outcomes)



Vasoactive agents (mortality outcomes)

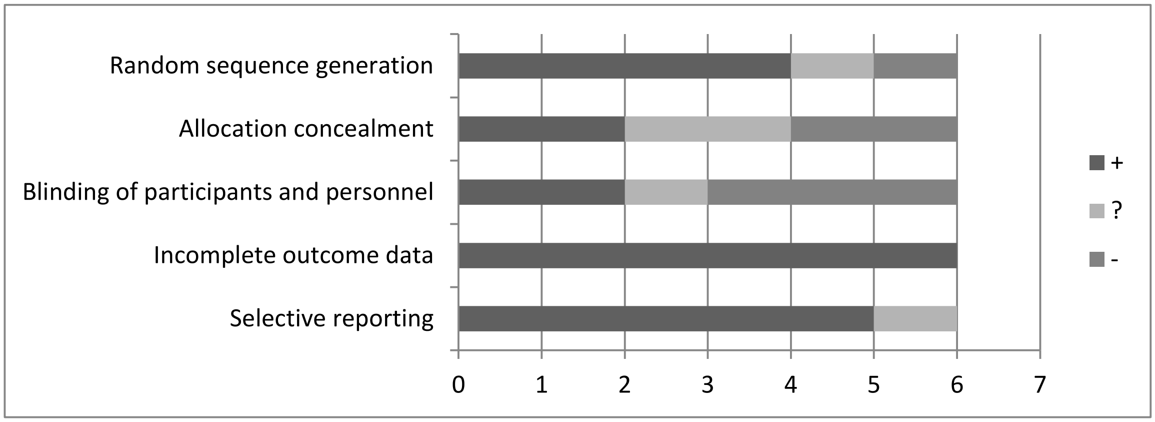


Vasoactive agents (length of stay outcomes)

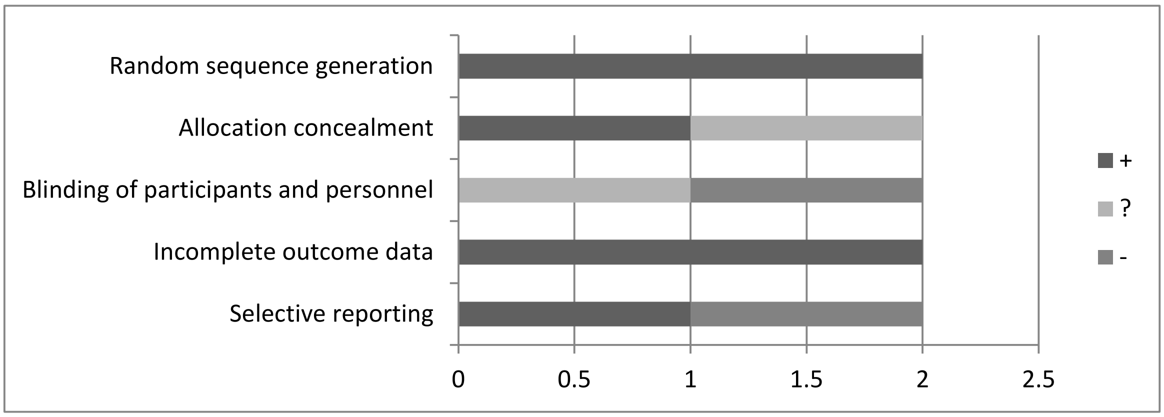


Antioxidants

Antioxidants (CIN outcomes)

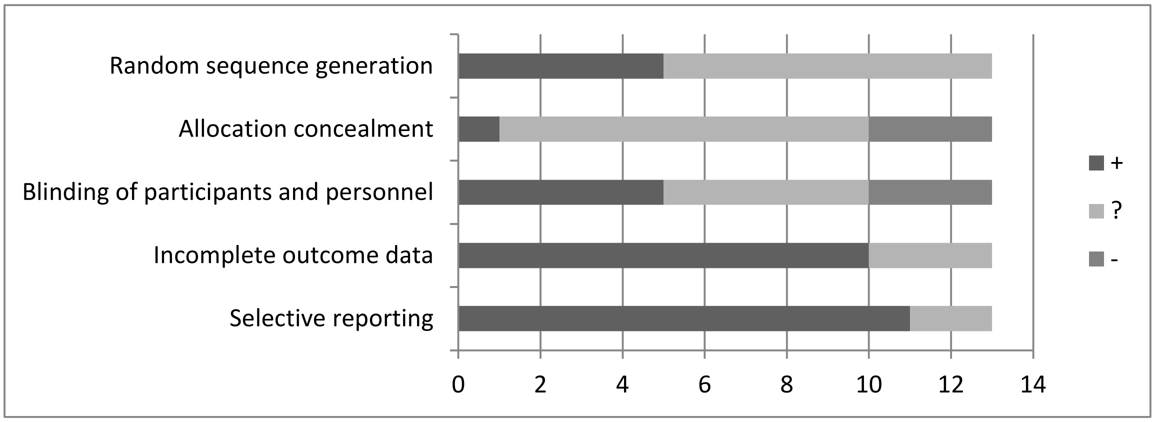


Antioxidants (renal replacement therapy outcomes)

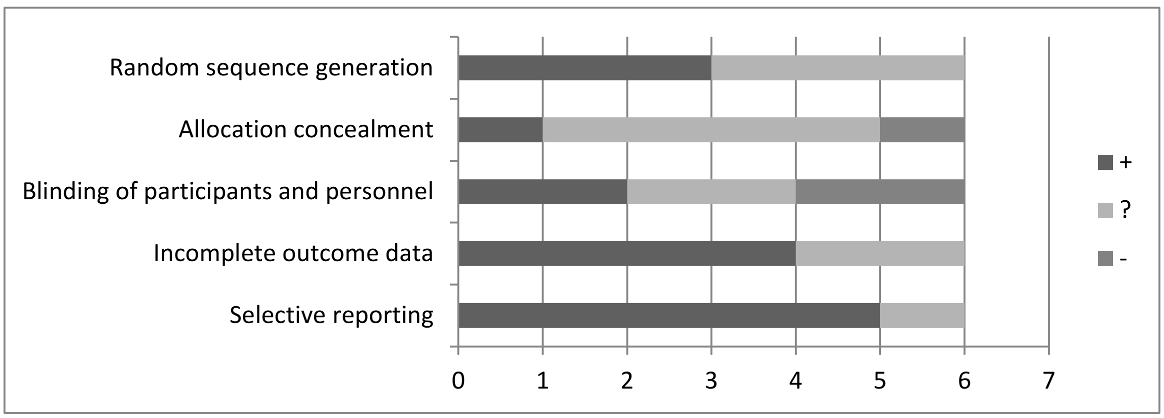


Fluids

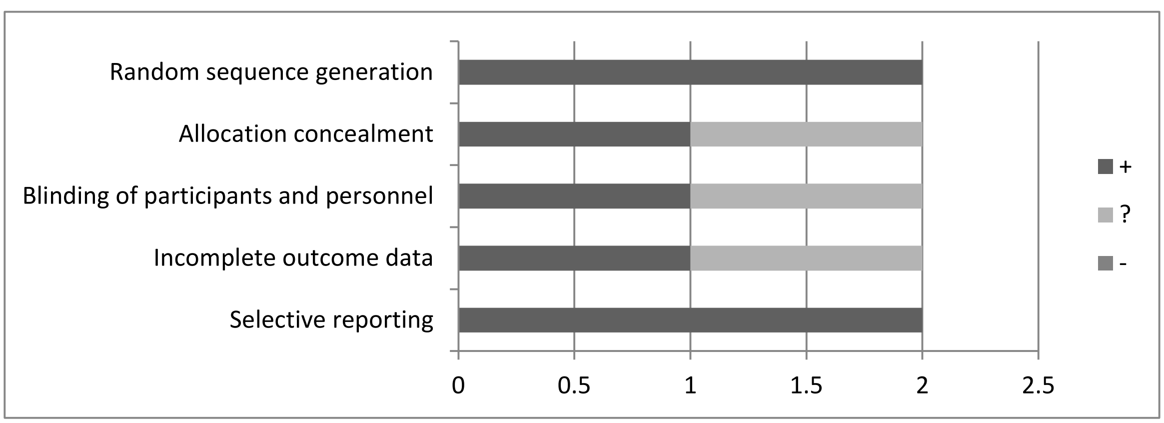
Fluids (CIN outcomes)



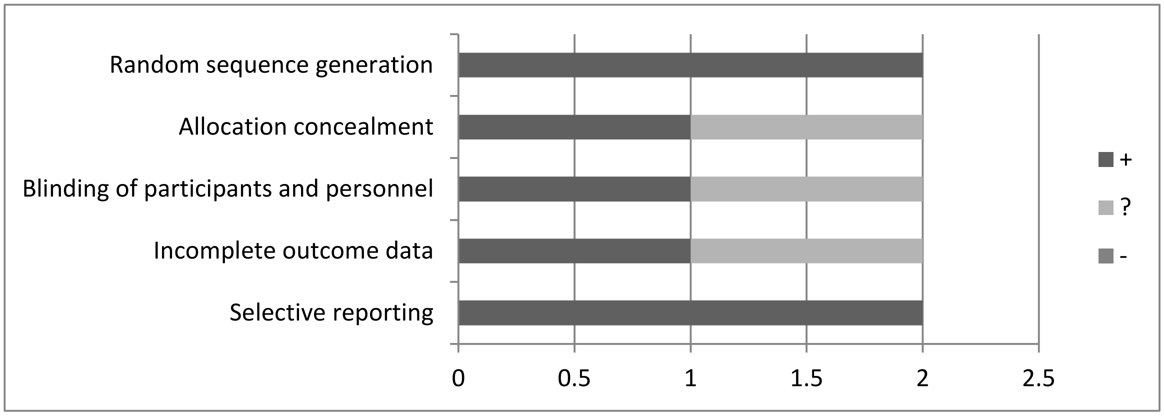
Fluids (renal replacement therapy outcomes)



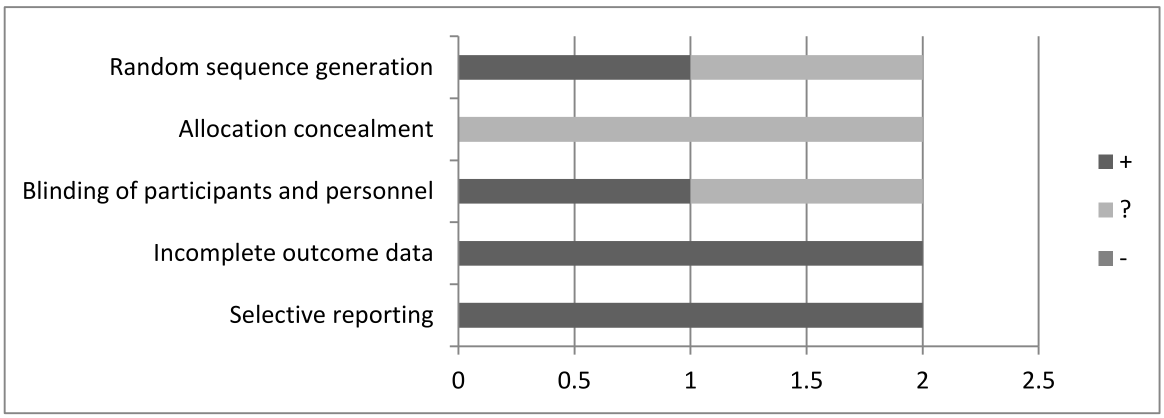
Fluids (cardiac outcomes)



Fluids (mortality outcomes)

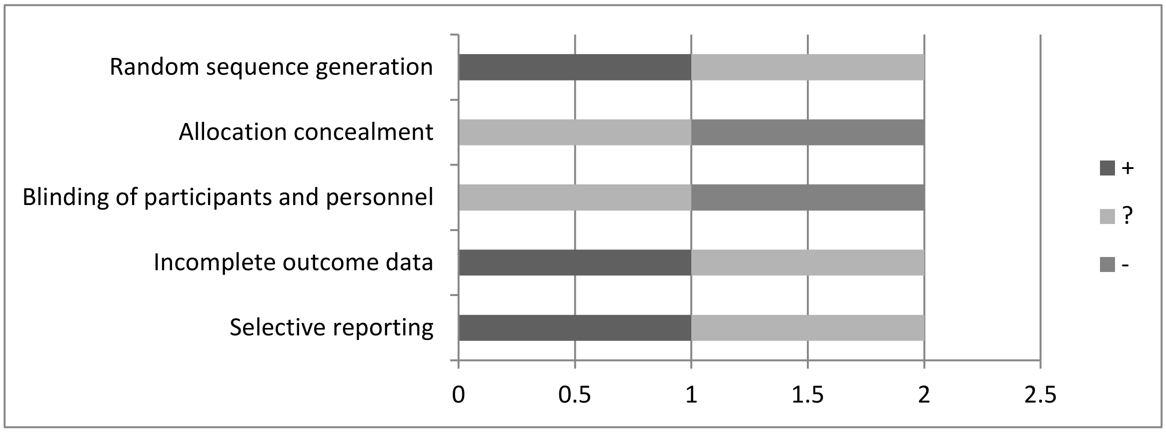


Fluids (length of stay outcomes)

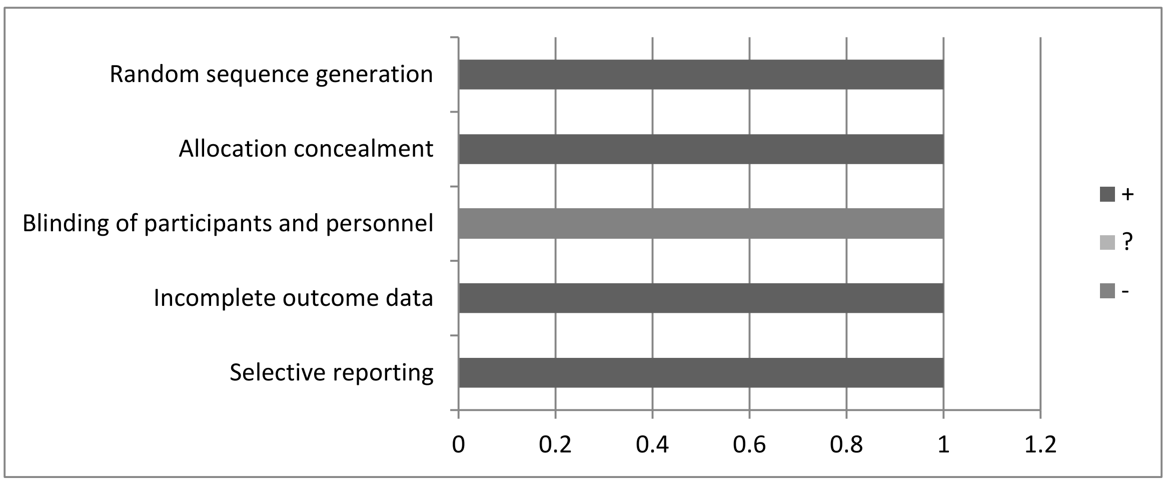


Dopamine

Dopamine (CIN outcomes)



Dopamine (renal replacement therapy outcomes)



Appendix H. Miscellaneous Comparisons

N-acetylcysteine Versus Other Interventions

A number of studies examined the potential effects of N-acetylcysteine compared with various other forms of potential prophylaxis. Most of these studies were addressed in other sections of this report, but they will also be briefly explored here.

Study Characteristics

We found 24 studies comparing N-acetylcysteine with other medications, IV fluids, and dialysis. In this group, N-acetylcysteine was compared with the following medications: ascorbic acid,[1, 2] nebivolol,[3] atorvastatin,[4] aminophylline,[5] theophylline,[6-8] fenoldopam,[9-11] allopurinol,[12] and misoprostol.[7]

N-acetylcysteine has been used in various doses with and compared against IV saline in various regimens, including with IV saline and compared with N-acetylcysteine plus IV sodium bicarbonate.[13, 14] In addition, IV saline and IV sodium bicarbonate with and without N-acetylcysteine have been compared to each other. [15, 16] Other studies compared N-acetylcysteine plus IV fluids with dialysis plus IV fluids[17] and to other variations of IV fluids,[14, 18-20] including as an arm in some of the studies that also compared N-acetylcysteine with other medications. Some studies compared two different doses of N-acetylcysteine to each other,[21-23], one study compared IV saline plus N-acetylcysteine postprocedure with IV bicarbonate plus N-acetylcysteine preprocedure and postprocedure [24], and one study compared IV saline plus N-acetylcysteine with allopurinol plus IV saline[12] (Appendix I, Evidence Tables I-1 to I-3, I-4).

The followup time for these 24 studies varied between 48 hours and 1316 days; most had a followup time of less than 5 days. The mode of contrast media administration in all studies was intra-arterial, except for one study that included both intra-arterial or IV contrast media administration.[7] Studies varied in terms of: doses of N-acetylcysteine; doses, type, and duration of IV fluids; sample size; and outcome time.

Some studies used a serum creatinine greater than 0.5 mg/dL in the definition of CIN, some used a serum creatinine greater than 25 percent, and some used both definitions. Because of the large study heterogeneity, a meta-analysis was not performed. In all cases, CIN was defined as occurring at either 48 or 72 hours, but in some cases, the incidence of CIN was also presented at later time points. Castini et al did not present the 48-hour CIN data in their paper; they provided this information to us via personal communication.[19]

Regarding the quality of the 24 studies, 11 had a high risk of bias, [3, 6, 12, 14, 16-18, 20, 24] one had a low risk,[1] and the remaining 13 had medium risk.[2, 4, 5, 9-11, 13, 15, 19, 21-23] All studies with high risk of bias had low scores in reporting of allocation generation, allocation concealment, and masking of subjects and/or investigators.[3, 6, 12, 14, 16-18, 20, 24]

Contrast Induced Nephropathy

Outcomes are presented in the evidence tables (Appendix I, Evidence Table I-5). Most of the studies included three treatment groups, and some of their outcomes are discussed in other sections. Some studies demonstrated a benefit of N-acetylcysteine, including the study by Heguilen et al.,[13] which demonstrated that the use of N-acetylcysteine (given with IV sodium bicarbonate or with IV saline) was associated with a statistically significant decrease in the occurrence of CIN when compared with IV sodium bicarbonate alone (OR 0.18, 95% CI, 0.04 to 0.72, p =0.016). In a study by Kinbara et al., no participants receiving N-acetylcysteine with IV saline or aminophylline with IV saline developed CIN, while 26.7 percent of participants in the group receiving only IV saline developed CIN (p = 0.01 across all arms). [5] In one of the studies by Briguori et al.,[10] the incidence of CIN was higher in patients who received IV saline with fenoldopam (13.7%) compared with those who received IV saline with N-acetylcysteine (4.1%, p = 0.019). A study by Kumar et al.[12] the incidence of CIN was higher in patients who received N-acetylcysteine, in comparison to the allopurinol arm (18 vs 0, p=NR).[12] A benefit of N-acetylcysteine was not consistent across all studies, although the comparator was not always the same in both groups. One study compared placebo plus IV normal saline, low-dose N-acetylcysteine (600 mg IV before contrast media administration, with 600 mg orally twice a day for 48 hours after the contrast media administration) plus normal saline, with high-dose N-acetylcysteine (1200 mg IV before contrast media administration followed by 1200 mg orally twice a day for 48 hours after the contrast media administration) plus normal saline.[22] The incidence of CIN was 33 percent in the placebo plus saline group, 15 percent in the low-dose N-acetylcysteine group, and 10 percent in the high-dose N-acetylcysteine group (p < 0.001 across all groups). In another study by Briguori, et al.[23] single-dose N-acetylcysteine (600 mg orally twice daily on the day before and day of contrast media administration) was also less successful than double-dose N-acetylcysteine (1200 mg orally twice daily on the day before and day of contrast media administration) at preventing CIN (11% versus 3.5%, p=0.38) (Appendix I, Evidence Table I-5).

In some studies, the comparator between groups was not N-acetylcysteine, but rather the type or presence of IV fluids. For example, Chen et al.[18] evaluated the effects of N-acetylcysteine with and without IV 0.45 percent saline in patients with serum creatinine greater than 1.5 mg/dL. There was a higher incidence of CIN in the group that did not receive IV fluids (34% versus 21%, p < 0.01). Chen, et al. was the only study of the 23 that used a comparator of no fluids and no medication. Briguori et al.[2] found that patients receiving IV sodium bicarbonate with N-acetylcysteine were less likely to develop CIN compared with those receiving N-acetylcysteine with IV saline (p=0.019). In a study by Reinecke et al., dialysis was also used as a comparator; patients receiving IV fluids with dialysis, for reasons that were unclear, were more likely to develop CIN than patients receiving IV fluids with N-acetylcysteine or IV fluids alone (0.008 across groups).[16] However, Reinecke et al. did demonstrate that after 30–60 days, most patients who had originally developed CIN had recovered even after undergoing hemodialysis. In addition, the percentage of patients with elevated serum creatinine concentrations at 30–60 days was similar in all treatment arms.

Finally, one of these studies compared the timing of N-acetylcysteine delivery. This study determined that IV saline with N-acetylcysteine plus IV normal saline postprocedure was less effective than IV sodium bicarbonate with N-acetylcysteine preprocedure and postprocedure (21.8% versus 1.8%, p= 0.0009) (Appendix I, Evidence Table I-5). [24] However, a different type of IV fluid was used in each group, which makes the results difficult to interpret.

In summary, when N-acetylcysteine was compared with interventions other than placebo or usual care, the strength of evidence was insufficient to support an overall conclusion regarding the potential effects of N-acetylcysteine compared with various other forms of potential prophylaxis because there was too much variation between studies in the comparisons and results. However, two studies provided direct evidence that a high dose of N-acetylcysteine was more effective than a low dose (Appendix I, Evidence Table I-5).

Other Outcomes

Twelve studies reported on other outcomes. Need for renal replacement therapy was discussed in nine of the studies, and none of these found a difference between groups. Six studies reported on a variety of cardiac outcomes.[6, 10, 11, 20, 22, 24] Only one of these studies showed lower incidence of cardiovascular outcomes in the group receiving N-acetylcysteine.[10] Ten studies reported on mortality as an outcome.[2, 6, 8, 10, 15-17, 21, 22, 24] One of these showed that patient recieivng N-acetylcysteine had a lower incidence of mortality.[22] One study reported on length of stay and reported a shorter length of stay in patients receiving N-acetylcysteins.[10] There was insufficient strength of evidence to conclude that N-acetylcysteine was more effective at improving the above outcomes. The evidence was insufficient because of the heterogeneity of the outcomes, imprecise results, and inconsistent reporting (Table H-1).

Table H-1. Summary of the strength of evidence: N-acetylcysteine versus other interventions

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN, short-term†	RCT: 24 (4563)	High	Direct	Inconsistent	Precise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from other interventions in preventing CIN
Need for RRT	RCT: 9 (1396)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from other interventions in preventing the need for RRT
Cardiovascular outcomes	RCT: 6 (799)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from other interventions in preventing cardiovascular events
Mortality	RCT: 10(2014)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from other interventions in reducing mortality
Length of stay	RCT: 1 (192)	Medium	Direct	NA	Imprecise	Insufficient	Insufficient strength of evidence to determine whether NAC plus IV saline differs from other interventions in reducing length of stay

CIN=contrast induced nephropathy; IV=intravenous; NA=not applicable; NAC=N-acetylcysteine; RCT=randomized controlled trial; RRT=renal replacement therapy

* Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores, the more conservative study limitation designation was chosen.
†Short-term is defined as within 7 days

Sodium Bicarbonate versus Other Interventions

Several studies compared the effects of IV sodium bicarbonate with various other forms of potential prophylaxis. Some of these studies are addressed in other sections, but are also discussed briefly here.

Study Characteristics

Our search identified four RCTs with a total study population of 773 that compared interventions of IV sodium bicarbonate with other interventions (besides placebo or saline hydration).[25-28] Contrast media included IOCM[28] and LOCM[25, 26, 29] and was administered intra-arterially in all studies. These studies were completed between 2009 and 2014 and were conducted in the United States,[25] Switzerland,[26] The Netherlands,[27] and Iran.[28] The mean age of patients in these studies ranged from 58 to 81. The percentage of patients with chronic kidney disease at baseline ranged from 24 to 100 percent, and the percentage of patients with diabetes mellitus ranged from 17 to 38 percent.

The comparison interventions included sodium bicarbonate versus acetazolamide,[28] long-term versus short-term IV sodium bicarbonate,[26] absence of hydration versus IV 1.4 percent sodium bicarbonate,[27] and IV sodium bicarbonate versus oral sodium bicarbonate (Appendix I, Evidence Tables I-1 to I-3, I-6).[25] All four of the studies addressing the efficacy of sodium bicarbonate compared with non-N-acetylcysteine based regimens had a medium risk of bias. These studies had low scores in regards to allocation sequence generation,[28] allocation concealment, [25, 26, 28] and masking of intervention.[25, 26] (Appendix I, Evidence Tables I-1 to I-3, I-6).

Because of the heterogeneity of the studies, a meta-analysis was not performed. A more detailed description of studies in this group and a summary of outcomes can be found in Appendices H and I.

Contrast Induced Nephropathy

Three of these four studies showed statistically significant results in relation to sodium bicarbonate versus other interventions.[26-28] In Kooiman et al. there was no difference in CIN between giving patients 1.4 percent sodium bicarbonate versus giving them no hydration at all (CIN events: 5% versus 6%, $p<0.001$).[27] Klima et al. had the same result when comparing short-term sodium bicarbonate exposure with long-term sodium bicarbonate exposure (CIN events: 9% versus 10%, $p=0.02$)[26] and comparing sodium bicarbonate with acetazolamide (CIN events: 4.2% versus 5.3%, respectively, $p=0.04$).[28] Comparing sodium bicarbonate plus IV saline hydration with sodium bicarbonate plus oral hydration showed no statistically significant difference ($p=0.525$)[25] (Appendix I, Evidence Table I-7).

The strength of evidence was low that sodium bicarbonate lowers the risk of CIN compared with interventions other than N-acetylcysteine, due to the heterogeneity of the reported effects of sodium bicarbonate, which were consistent but imprecise, the magnitude of effect, which was weak, and the study limitations, which were moderate (Table H-2).

Other Outcomes

Of the three studies that reported on outcomes of interest besides CIN,[25, 27, 28] only Cho et al. included reportable events for length of hospitalization. They did not find a significant difference between the arms with mean stays of approximately 4 days for all arms (p=0.657).[25] Cho et al. also reported no all-cause mortality events during the followup period.[25] The other two studies, Kooiman et al. and Pakfetrat et al., reported need for RRT and cardiac events, and both had no events during the followup period.[27, 28]

Due to the low number of studies reporting on other adverse outcomes, there is insufficient strength of evidence to support any conclusion on the effect of sodium bicarbonate intervention compared with other non-N-acetylcysteine interventions. (Table H-2)

Table H-2. Summary of the strength of evidence: Sodium bicarbonate versus other interventions

Outcome	Study design: No. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence*	Summary of key outcomes
Development of CIN Short-term†	RCT: 4	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that sodium bicarbonate decreases the risk of CIN compared with other interventions.
Need for RRT	RCT: 1	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Cardiovascular outcomes	RCT: 1	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion
Mortality	RCT: 1	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion

CIN=contrast induced nephropathy; IOCM=iso-osmolar contrast medium; LOCM= low-osmolar contrast medium; NA=not assessed; NR=not reported RCT=randomized controlled trial; RRT=renal replacement Therapy

* Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. In the instance where there is a split between study limitation scores, the more conservative study limitation designation was chosen.
†Short-term is defined as within 7 days

N-acetylcysteine Plus Sodium Bicarbonate Versus Other Interventions

A combination of sodium bicarbonate and N-acetylcysteine may help reduce CIN. The sodium bicarbonate expands the intravascular volume and may also offer protection against free radicals by alkalinization; it has also been proposed that the N-acetylcysteine may prevent vasoconstriction and the generation of free radicals.

Study characteristics

Our search identified six RCTs[2, 13, 14, 30-32] and one observational study,[33] with a total study population of 1805. These studies compared N-acetylcysteine plus sodium bicarbonate with interventions that were not placebo or saline hydration. Contrast media included IOCM[2, 14, 30-33] and LOCM.[13, 33] Contrast media were administered intra-arterially in all studies. These studies were completed between 2007 and 2013 and were conducted in the United States,[14] Italy,[2, 30, 32] and Argentina,[13] France,[31] plus one study that was completed between several North American centers.[33] The mean age of patients in these studies ranged from 64 to 76. The study population for all trials included patients with renal dysfunction who were undergoing coronary interventions or another major arteriographic procedure. Three of the studies only included patients with Stage 3 to Stage 4 chronic kidney disease.[13, 30, 31] (Appendix I, Evidence Tables I-1 to I-3, I-8)

Our search identified one observational study with a total study population of 262 that compared N-acetylcysteine plus sodium bicarbonate with N- acetylcysteine plus intravenous saline. The contrast media administered iopamidol.[34] This study was published in 2012 and was conducted in Italy. The mean age of patients ranged from 63 to 65. All patients had chronic kidney disease at baseline, and 55 to 61 percent of the patients had diabetes mellitus (Appendix I, Evidence Table I-8).

Contrast Induced Nephropathy

All of the studies reported a statistically significant difference in the incidence of CIN between the N-acetylcysteine plus sodium bicarbonate regimen and the other interventions.[2, 13, 14, 30-33] In Briguori et al. (2011) the results showed that the N-acetylcysteine plus sodium bicarbonate regimen was inferior to the RenalGuard regimen, both clinically and statistically.[30] Briguori et al. (2007), Heguilen et al., and Ratcliffe et al. reported the potential clinical superiority of N-acetylcysteine plus sodium bicarbonate over sodium chloride plus N-acetylcysteine.[2, 13, 14] The difference found in Briguori et al. was both clinically and statistically significant across several CIN definitions: Creatinine greater than 25 percent, Creatinine change greater than 0.5mg, and eGFR increase greater than 25 percent. However, when examining the same comparisons, Maioli et al. reported a potentially clinically but not statistically significant difference of sodium chloride plus N-acetylcysteine over N-acetylcysteine plus sodium bicarbonate.[32] Similar differences were reported when N-acetylcysteine plus sodium bicarbonate was compared with a placebo plus sodium bicarbonate[31] or the combination of sodium chloride plus ascorbic acid plus N-acetylcysteine.[32]

According to Heguilen et al.,[13] N-acetylcysteine plus sodium bicarbonate reduced CIN by a clinically important margin that was not statistically significant when compared with sodium bicarbonate, but no such difference was reported by Maioli et al.[32] (Appendix I, Evidence Table

I-9). Due to study heterogeneity, the strength of evidence was low for determining whether or not the addition of N-acetylcysteine to IV sodium bicarbonate decreases the risk of CIN due to medium study limitations and inconsistency; however, there was precision in the effect estimates (Appendix I, Evidence Table I-9).

The results of the observational study generally were similar to those reported in the RCTs when comparing the risk of CIN using N- acetylcysteine plus sodium bicarbonate with N-acetylcysteine plus intravenous saline (Appendix I, Evidence Table I-9).[34]

Other Outcomes

When the need for RRT was assessed in patients receiving N-acetylcysteine plus sodium bicarbonate and compared with those on the RenalGuard regimen, a difference was seen that could be clinically important; however, it was not statistically significant because of the small number of events.[30] Likewise, none of the studies were large enough to find a statistically significant difference in mortality, adverse cardiac events, or duration of hospitalization when comparing N-acetylcysteine plus sodium bicarbonate with any of the interventions because of the small number of events (Appendix I, Evidence Table I-9). The strength of evidence was low or insufficient for these outcomes as the risk of bias was medium and generally contained inconsistent or imprecise results (Table H-3).

Table H-3. Summary of the strength of evidence: N-acetylcysteine plus sodium bicarbonate versus other interventions

Outcome	Study design: No. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence*	Summary of key outcomes
Development of CIN short term†	RCT: 7	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that NAC plus sodium bicarbonate decreases the risk of CIN compared with other interventions.
Need for RRT	RCT: 5	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that NAC plus sodium bicarbonate decreases the need for RRT compared with other fluid interventions.
Cardiovascular outcomes	RCT: 2	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that NAC plus sodium bicarbonate decreases the risk of cardiac events compared with other interventions.
Mortality	RCT: 2	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that NAC plus sodium bicarbonate decreases the risk of mortality compared with other interventions.
Adverse events	RCT: 4	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence that NAC plus sodium bicarbonate decreases the risk of other adverse events compared with other interventions.

CIN=contrast induced nephropathy; IOCM=iso-osmolar contrast medium; LOCM= low-osmolar contrast medium; NA=not assessed; NR=not reported RCT=randomized controlled trial; RRT=Renal Replacement Therapy

* Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. Where there is a split between study limitation scores, the more conservative study limitation designation was chosen.
†Short-term is defined as within 7 days

Diuretics Versus Other Interventions

As a result of several proposed benefits, diuretics have been investigated as possible prophylaxis for CIN: (1) reducing the duration of nephron exposure to the contrast media via forced dieresis; (2) protecting against medullary ischemia; and (3) allowing for increased concurrent hydration as a result of decreased concern of over hydration and pulmonary edema. However, the use of diuretics alone without concurrent hydration is shown to be detrimental because excessive diuresis is found to aggravate hypoperfusion, vasoconstriction, and viscosity, all of which can lead to an increased risk of CIN.[35] Here, we review the effectiveness of using diuretics without concurrent hydration.

Study Characteristics

We found three studies comparing the use of different diuretics (furosemide, mannitol, and acetazolamide) in combination with IV saline to prevent CIN.[28, 36, 37] All studies included patients undergoing cardiovascular interventions and patients with diabetes mellitus. Two studies used LOCM and one used IOCM. Two evaluated furosemide as the diuretic of interest[36, 37] and also used it as a single comparator. Diuretic administration was given intravenously in all three of the studies, but the protocols and doses varied. One study evaluated the effects of mannitol,[37] and another included acetazolamide. Due to the substantial heterogeneity of the comparators and follow-up periods, a meta-analysis was not performed.

All studies had medium risk of bias and were limited by problems with allocation generation, allocation concealment, and incomplete outcome reporting.

Contrast Induced Nephropathy

The results on the use of furosemide are conflicting and suggest its effect is dose-dependent; while lower doses seem to have a protective effect against the development of CIN (p=0.005, RR 0.29 95% CI, 0.10 to 0.85),[36] higher doses seem to have a deleterious effect (40% versus 11%, p=0.02). [37] Overall, the use of mannitol and acetazolamide did not offer any protection against the development of CIN.[28, 37] Patients presented similar rates of complications and need for RRT in both of the groups in the studies reporting this outcome.[36, 37] In addition, mannitol did not offer any protection against the development of CIN. When mannitol was used alone, patients had higher rates of CIN than patients receiving IV saline (28% versus 11%) but less than those receiving furosemide (28% versus 40%); none of these differences were statistically significant.[37] The single study on the use of acetazolamide compared with IV saline showed a clinically important and statistically significant benefit (5.3% versus 12.5%, p=0.04) (Appendix I, Evidence Table I-12).[28] A more detailed description of the studies in this group and a summary of outcomes can be found in Appendices H and I.

Overall, the strength of evidence was insufficient to support a conclusion about the effectiveness of any diuretic in preventing CIN because the effects of diuretics were inconsistent and imprecise, the magnitude of effect was weak, and the studies had medium risk of bias (Table H-4).

Other Outcomes

The use of furosemide did not indicate a statistically significant difference when compared with IV saline and evaluating other clinical outcomes because of infrequent events; however, the effect sizes demonstrated a potential clinical significance. Patients presented similar rates of complications and need for RRT in both of the groups in the studies reporting these outcomes. Overall, there was insufficient strength of evidence to support a conclusion about the effects of furosemide on other clinical outcomes. (Table H-4; Appendix I, Evidence Table I-12).[36, 37]

Table H-4. Summary of the strength of evidence: diuretics versus intravenous saline

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN in the short term*	RCT: 3 (534)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of diuretics on the risk of CIN
Need for RRT	RCT: 2 (248)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of diuretics on the need for RRT
Cardiac events	RCT: 1 (170)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of diuretics on the risk of cardiac events
Mortality	RCT: 1 (170)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of diuretics on the risk of mortality

CIN=contrast-induced nephropathy; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy
*Short-term is defined as within 7 days

Vasoactive Agents Versus Other Interventions

Persistent arterial vasoconstriction may lead to direct tubular toxicity, medullar ischemia, and even cellular damage. The use of vasoactive agents in preventing CIN may antagonize the contrast media's toxic effect by increasing the flow, but the renoprotective effect can vary according to the mechanism of action of each vasodilator.[38, 39]

Study Characteristics

We found 12 studies comparing vasoactive agents with other interventions: four studies on fenoldopam,[9-11, 40] three on prostaglandin E1 (PgE1) (one using misoprostol,[7] one using alprostadil,[41] and one using pure PgE1,[42] two on calcium antagonists (one with nifedipine),[7] and one with the combination of amlodipine and valsartan, an angiotensin receptor blocker),[43] one on benazepril (an ACE inhibitor),[44] and one on nebivolol (a beta blocker).[3] Included in this number are two studies that investigated the need to suspend the intake of ACE/ARB before receiving contrast media.[45, 46] One of these two studies included only patients undergoing CT imaging and using IV contrast.[7] The other included patients undergoing cardiovascular interventions and using intra-arterial contrast. These studies were completed between 2002 and 2014, and were conducted in the United States,[9, 11, 40] Italy,[10] Turkey,[3, 7, 43] China,[41, 42, 44] and Israel.[46]

Our search identified one observational study, with a total study population of 5299, which compared the use of intervention ACE inhibitors with the absence of ACE inhibitors. Contrast media included iodixanal administered intra-arterially.[47] This study was published in 2012 in Korea. The mean age of patients ranged from 60 to 62 years old. All patients had chronic kidney disease at baseline, and the percentage of patients with diabetes mellitus ranged from 34 to 46 percent (Appendix I, Evidence Tables I-1 to I-3, I -13).

All 13 studies included patients with diabetes mellitus, but only one performed subgroup analysis for this population.[10] Five studies used LOCM, five used IOCM, one used both IOCM and LOCM, and one did not specify the type of contrast media used. The studies were very heterogeneous, from the medications included and the comparisons made to the doses used.

Four studies had high risk of bias,[7, 41, 42, 46] four had medium risk of bias,[3, 11, 44, 45] and four had low risk of bias.[9, 10, 40, 43] Limitations were seen in all domains.

Contrast Induced Nephropathy

In the three studies that compared fenoldopam with low doses of N-acetylcysteine or IV saline, there were no differences in the incidence of CIN.[9-11] However, when the N-acetylcysteine dose was increased and fenoldopam was given at comparable doses, a lower incidence of CIN was observed in the N-acetylcysteine arm, with a statistically significant difference at the highest dose (4800 mg; 13.7% versus 4.1%, OR 0.27, 95% CI, 0.08 to 0.85).[10] The effect was reversed when fenoldopam was given intrarenally (11.5% in the intrarenal fenoldopam group versus 30% in the no-fenoldopam control group, RR 0.38, 95% CI, 0.16 to 0.88)[40] (Appendix I, Evidence Table I-14).

The use of calcium channel blockers showed conflicting results. Nifedipine seemed to be at least as effective as IV saline, but more effective than N-acetylcysteine in protecting against CIN (0% in nifedipine and IV saline groups versus 5% in N-acetylcysteine groups, p=NS);[7] amlodipine plus valsartan appeared to increase the risk of CIN without being statistically significant (17.8% versus 6.7%, p=0.20).[43]

Patients receiving benazepril seemed to have a lower incidence of CIN, but the results were not statistically significant (3.5% versus 9.7%, p=0.51).[44] Conversely, the use of nebivolol did not show a clinically important or statistically significant difference (Appendix I, Evidence Table I-14).

Overall, the strength of evidence was insufficient to support a conclusion about the effectiveness of vasoactive agents in preventing CIN. In these studies, the results were inconsistent and imprecise but direct, the magnitude of effect was weak, and the study limitations were high.

Generally, the results of the observational study that compared ACE inhibitors with the absence of an ACE inhibitor were similar to those reported in the RCTs; however, the drugs used were different.[47]

Other Outcomes

Few articles reported on secondary clinical outcomes. The studies reporting complications did not report a statistically significant difference between arms. The numbers of complications were higher in the fenoldopam arm compared with the N-acetylcysteine arm, but they were not statistically significant, since the numbers were very low and very similar in all intervention arms (Appendix I, Evidence Table I-14). In general, the differences between vasoactive agents and their comparators were not significant, and the data were insufficient to draw any conclusions (Table H-5).

Table H-5. Summary of the strength of evidence: adenosine antagonists plus intravenous saline versus intravenous saline

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN in the short term†,* (meta-analysis)	RCT: 11 (1456)	High	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of the evidence about the effect of vasoactive agents on preventing CIN.
Need for RRT	RCT: 5 (684)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of vasoactive agents on the need for RRT
Mortality	RCT: 3 (464)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of vasoactive agents on the risk of mortality
Length of stay	RCT: 4(425)	Medium	Direct	Inconsistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of vasoactive agents on the length of stay

CIN=contrast-induced nephropathy; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy

* Includes studies examined in meta-analysis because of comparability of intervention and control arms
†Short-term is defined as within 7 days

Antioxidants Versus Hydration

Contrast media has a direct cytotoxic effect in the kidney as it generates the formation of reactive oxygen species. The use of antioxidants has been evaluated to assess the possibility of reducing the incidence of CIN by counteracting the damage caused by the free radicals produced.

Study Characteristics

We found seven studies evaluating different antioxidant strategies for preventing CIN. The antioxidant probucol was evaluated in two of these studies,[48, 49] while two investigated pentoxifylline, an antioxidant and anti-inflammatory agent,[50, 51] and the other two investigated sodium-2 mercaptoethanesulfonate (MESNA), a scavenger of reactive oxygen species,[52] zinc, which has the potential to act as an “endogenous antioxidant” via increasing metallothionein, [53] and trimetazidine an antianginal agent which decreases free radicals, decreases oxygen consumption and may also decrease renal ischemia.[54] All were conducted in patients with impaired renal function (serum creatinine greater than 1.2 and less than 3.0 mg/dl) undergoing coronary interventions, and all studies used LOCM except one that used IOCM[51] (Appendix I, Evidence Tables I-1 to I-3, I-16, I-17).

Contrast Induced Nephropathy

The studies on antioxidants were too heterogeneous to include in a meta-analysis, but we show the study results in Figure H-1. Although zinc did not prevent CIN in the study by Kimmel, the other studies that evaluated the effects of antioxidants demonstrated a lower incidence of CIN in the intervention arm when compared to standard hydration, but not all results were statistically significant. The incidence of CIN was lower in the probucol group when compared to hydration (4.2% vs 21.3% , P<0.01[49] and 7.8% vs 14.5% , P =0.13[48]). Patients given MESNA also had a lower incidence of CIN compared to placebo (0 vs 14%, P=0.005)).[52] For patients given pentoxifylline, results were contradictory; while Firouzi et al showed a not statistically significant renoprotective effect (8.5% vs 13.7%, P=0.17),[50] Yavari et al found a non-significant difference in the CIN incidence only in the hypertensive population. (6.2% vs 5.9% in the general population and 5% vs 8.7% in the hypertensives). [51] While Shethata et al. also showed a decreased incidence of CIN in the arm receiving trimetazidine (12% vs 28%, p<0.05), these results are not comparable since both arms also received N-Acetylcysteine.[54](Figure H-1; Appendix I, Evidence Tables I-16, I-18).

Overall, the strength of evidence was insufficient to support a conclusion about the effectiveness of antioxidants in preventing CIN due to the heterogeneity of the studies with results that were inconsistent and imprecise but direct, with weak magnitude of effect and high study limitations. Five studies had low risk of bias, [49, 51-54] one had medium risk of bias,[50] and one had high risk of bias.[48] Studies were limited by problems with allocation generation[48, 53], allocation concealment, [48-50, 53] and intervention concealment[48-51].

Other Outcomes

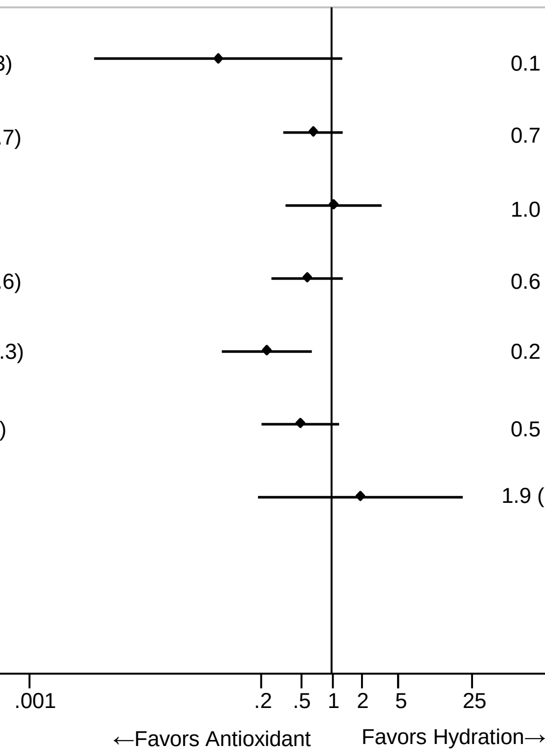
The two studies analyzing additional outcomes reported that no patients required further renal replacement therapy, none died in the hospital, and none required prolonged hospitalization. The data was insufficient to draw any conclusions on the other outcomes (Appendix I, Evidence Tables I-17, I-19).

Other Comparisons

Two studies reported on need of RRT, cardiovascular morbidity and length of hospitalization, and they both reported no events in both arms.[50, 54] (Appendix I, Evidence Tables I-17, I-19). Both studies had a high risk of bias. The risk of bias was high because of problems with allocation generation and concealment and they both had incomplete data (Table H-6).

Figure H-1. Analysis of antioxidants versus hydration for the prevention of contrast induced nephropathy.

Author, year	Contrast	Antioxidant	Hydration	CIN events, N (%) Antioxidant	CIN events, N (%) Hydration	RR (95% CI)
Ludwig, 2011[51]	LOCM	MESNA	Hydration	0 (0)	7 (14.3)	0.1 (0.0, 1.3)
Firouzi, 2012[49]	LOCM	Pentoxifylline	Hydration	12 (8.6)	20 (13.7)	0.7 (0.3, 1.3)
Yavari, 2014[50]	IOCM	Pentoxifylline	Hydration	6 (6.2)	6 (5.9)	1.0 (0.3, 3.1)
Li, 2009[47]	LOCM	Probucol	Hydration	8 (7.8)	15 (14.6)	0.6 (0.3, 1.3)
Yin, 2013[48]	LOCM	Probucol	Hydration	4 (4.2)	23 (21.3)	0.2 (0.1, 0.6)
Shehata, 2014[53]	LOCM	Trimetazidine + NAC	Hydration + NAC	6 (12)	14 (28)	0.5 (0.2, 1.2)
Kimmel, 2008[52]	LOCM	Zinc	Hydration	2 (7.4)	1 (3.7)	1.9 (0.2, 20.1)



Risk Ratio and 95% Confidence Intervals

%=percent; CI=confidence interval; CIN=contrast induced nephropathy; LOCM=low-osmolar contrast media; MESNA= sodium 2-mercaptoethanesulfonate; N=sample size; OR=odds ratio

Table H-6. Summary of the strength of evidence: antioxidants versus intravenous saline

Outcome	Study design: no. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence	Summary of key outcomes
Development of CIN in the short term†,* (meta-analysis)	RCT: 7 (1147)	Low	Direct	Inconsistent	Imprecise	Low	The strength of the evidence is low that antioxidants are effective in preventing CIN.
Need for RRT	RCT: 2 (386)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of antioxidants on the need for RRT
Mortality	RCT: 2 (386)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of antioxidants on the risk of mortality
Length of stay	RCT: 2(386)	High	Direct	Consistent	Imprecise	Insufficient	Insufficient strength of evidence about the effect of antioxidants on the length of stay

CIN=contrast-induced nephropathy; N=sample size; NA=not applicable; RCT=randomized controlled trial; RRT=renal replacement therapy

* Includes studies examined in meta-analysis because of comparability of intervention and control arms
†Short-term is defined as within 7 days

Fluids Interventions

One possible mechanism underlying CIN is hypoperfusion, which can potentially result from vasoconstriction. Based on this outcome, volume expansion with fluids, which could improve hypoperfusion, has been postulated as a possible intervention for CIN.

Study Characteristics

Our search identified 13 RCTs and one observational study[55], with a total study population of 5029, which compared intervention hydration strategies with other hydration strategies. Contrast media included IOCM[18, 56-58] and LOCM[25, 59-64] and was administered intra-arterially in all studies. The RCTs were completed between 2002 and 2014 and were conducted in Germany,[59, 63] the United States,[25, 60, 64, 65] China,[18, 62] Turkey,[61] Canada,[66] Italy,[56, 57] and Spain.[58] The mean age of patients in these studies ranged from 54 to 80 years of age. The observational study was published in 1980 and was conducted in the United States.[55] (Appendix I, Evidence Tables I-1 to I-3, I-20).

The study populations varied across studies. However, most included adults without renal impairment who were undergoing cardiovascular interventions. Four studies included patients with some degree of renal impairment,[60, 61, 65, 66] and three only included patients with acute myocardial infarction.[18, 56, 57] These studies were published from 1999 to 2014 (Appendix I, Evidence Tables I-1 to I-3, I-20).

All of these studies defined CIN as either an increase in serum creatinine by 25 percent or as a change in serum creatinine of 0.5 mg from baseline at 48 or 72 hours. However, one study also used an increase of glomerular filtration rate from a baseline of 50 percent,[59] and another recorded any CIN event between one and four days.[60]

The secondary outcomes we evaluated in these studies included mortality,[18, 56, 60] need for renal replacement therapy,[56, 59, 60, 64, 65] length of hospitalization,[25, 63, 65] and major cardiac adverse events[56, 60, 63] (Appendix I, Evidence Tables I-1 to I-3, I-21).

Nine of the 13 RCTs had a medium risk of bias. In those studies, the risk of bias was medium because of problems with allocation generation and concealment, as well as incomplete data and selective outcome reporting.

Contrast Induced Nephropathy

In these studies, fluids given prior to contrast media administration were found to be superior to no fluids given. The same was true when a stratified analysis was performed on patients with a left ejection fraction of less than 40 percent.[56] However, Chen et al. reported equivalent CIN outcomes for fluids versus no fluids in patients without renal impairment; the fluid administered in the Chen et al. study was 0.45% saline. The incidence of CIN for patients who received precontrast and postcontrast media fluids was similar to those only given fluids during the procedure.[59, 62] In Manari et al.,[57] the incidence of CIN (using the creatinine definition if an increase in serum creatinine of 25% or greater) was comparable between participants given normal saline hydration and those given high-dose normal saline (Standard dose: 19.2% versus high-dose hydration: 19%, p=0.92). A similar result was observed when using the creatinine definition of an increase of 0.5 mg/dL or greater (4.6% versus 5.6%, p=0.51 respectively).[57] However, in Brar et al., comparison between IV normal saline and left ventricular end diastolic pressure-guided IV hydration showed a significant decrease in CIN incidence in favor of left ventricular end diastolic pressure -guided hydration, especially when CIN was measured by the definitions of either greater than 25% or a greater than 0.5mg/dl increase in serum creatinine from baseline (16.3% versus 6.7%, p=0.005).[60]

Kong et al., which compared preprocedure or postprocedure oral fluids with normal 0.9% IV saline hydration did not find any difference in the incidence of CIN (all arm comparison p=0.86).[62] Moreover, Maioli et al. found that normal saline given before contrast media administration was superior to normal saline after contrast media administration (12% CIN with early fluids versus 22.7% CIN with late fluids, p=0.001).[56] Cho et al. reported findings that varied depending on the fluids used (22.2% CIN for IV normal saline versus 9.1% CIN for oral fluids p=0.63; and 9.5% for IV sodium bicarbonate versus 4.7% for oral sodium bicarbonate, p=0.53).[25] Trivedi et al.[64] reported better outcomes for patients who received IV normal saline compared with those receiving oral fluids (2% CIN for IV saline versus 7% CIN for oral fluids, p=0.005). Similarly, the outcomes for patients receiving hypotonic and isotonic saline were comparable. However, addition of 5 percent glucose to hypotonic saline was found to be inferior to isotonic saline in preventing CIN; this was especially true for women and people with diabetes mellitus (Appendix I, Evidence Table I-21).[63]

Overall, the strength of evidence was low to support a conclusion about the effectiveness of different fluids used in preventing CIN due to the heterogeneity of the studies; different fluid regimens were compared across studies, which limited the overall the strength of evidence. Additionally, results were inconsistent but imprecise and direct, the magnitude of effect was weak, and the study limitations were medium (Table H-7).

The one observational study reported no instance of renal failure when proper hydration was maintained.[55] The reported results were similar generally to those reported in RCTs regarding hydration, but as there was no comparison of different hydration methods in the observational study, this did not affect the grading of the strength of evidence for the RCTs.

Other Outcomes

Only one study[60] reported any statistical difference between the fluid intervention groups by mortality, need for RRT, duration of hospitalization stay, or adverse cardiac events. This study[60] showed a statistically significant difference for all-cause mortality at six months followup (Standard 0.9% saline arm: 8/200 (4%); left ventricular end diastolic pressure -guided hydration arm: 1/196 (0.5%), p=0.04), although at 30 days followup for all-cause mortality, the incidence of events was non-significant (p=0.25).

Overall, few studies reported on these outcomes, with most reporting an incidence of very similar events in all arms. The data is insufficient to draw any conclusion about the comparative effects of different fluids on these other outcomes (Appendix I, Evidence Table I-21).

Table H-7. Summary of the strength of evidence: Fluid interventions

Outcome	Study design: No. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence*	Summary of key outcomes
Development of CIN in the short term†	RCT: 13	Medium	Direct	Inconsistent	Precise	Low	Low strength of evidence that fluid interventions decrease the risk of CIN compared with other fluid interventions.
Need for RRT	RCT: 6	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that fluid interventions decrease the need for RRT compared with other fluid interventions.
Cardiovascular outcomes	RCT: 3	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that fluid interventions decrease the risk of cardiac events compared with other fluid interventions.
Mortality	RCT: 3	Medium	Direct	Consistent	Imprecise	Low	Low strength of evidence that fluid interventions decrease the risk of mortality compared with other fluid interventions.
Adverse events	RCT: 8	Medium	Direct	Inconsistent	Imprecise	Insufficent	Insufficient evidence that fluid interventions impact the risk of other adverse events compared with other fluid interventions.

CIN=contrast-induced nephropathy; IOCM=iso-osmolar contrast medium; LOCM= low-osmolar contrast medium; NA=not assessed; NR=not reported RCT=randomized controlled trial; RRT=renal replacement Therapy

* Due to the heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. Where there is a split between study limitation scores, the more conservative study limitation designation was chosen.
†Short-term is defined as within 7 days

Dopamine Versus Other Interventions

Increasing renal blood flow may help prevent CIN. Dopamine, a potent vasodilator, has been suggested as a possible intervention for the reduction of CIN, especially among patients with impaired renal function.[67]

Study Characteristics

Our search identified two RCTs[68, 69] and one observational study[70] with a total study population of 337, which compared dopamine with a variety of interventions.

In all studies, the contrast media used was LOCM and was administered intra-arterially. These studies were completed between 1992 and 1999 and were all conducted in the United States. The mean age of patients in these studies ranged from 64 to 75 years old. The percentage of patients with chronic kidney disease at baseline ranged from 56.8 to 100 percent and the percentage of patients with diabetes mellitus ranged from 9.8 to 12 percent.

In both RCTs, dopamine was administered before and after contrast media. Hans et al. compared dopamine with a placebo[69] and Abizaid et al. compared dopamine with saline and aminophylline.[68] The dose of dopamine in the two studies was 2.5 microgram/kg/min (Appendix I, Evidence Tables I-1 to I-3, I-23).[68, 69]

Contrast-Induced Nephropathy

For both RCTs, CIN was defined as either a change in serum creatinine by 25 percent or greater than 0.5 mg from baseline. In Abizaid et al., the effectiveness of dopamine in preventing CIN was compared with giving IV saline and aminophylline, with no statistically significant difference.[68] Hans et al. reported the superiority of dopamine over a placebo in preventing CIN at 24 hours, 48 hours, 72 hours, and 96 hours, and this was statistically significant.[69] These studies evaluated other outcomes, including the need for RRT and length of hospitalization (Table H-8).[68]

These two studies had varying limitations, one with high risk of bias and one with medium risk of bias. The two also had problems with allocation generation and concealment, and one had incomplete data and selective outcome reporting. The strength of evidence was insufficient to support a conclusion about the effectiveness of dopamine relative to other interventions due to the study limitations and low number of the included studies (Table H-8, Appendix I, Evidence Table I-23).

The results of the observational study were generally similar to those reported in the RCTs with regard to affect of dopamine on CIN incidence compared with no dopamine. While there was a difference in CIN incidence in favor of the dopamine group, it was not statistically significant.

Other Outcomes

No difference was observed between dopamine and any of the other treatments in terms of need for RRT and length of hospitalization after contrast media administration. The number of events was low and comparable in all arms (Appendix I, Evidence Table I-24). The strength of evidence was insufficient to support a conclusion about the effectiveness of dopamine relative to other interventions, as only Abizaid et al. reported on secondary outcomes.

Table H-8. Summary of the strength of evidence: dopamine versus other interventions

Outcome	Study design: No. studies (N)	Study limitations	Directness	Consistency	Precision	Strength of evidence*	Summary of key outcomes
Development of CIN in the short term†	RCT: 2 (127)	High	Direct	Consistent	Imprecise	Insufficient	Insifficient strength of evidence that dopamine decreases the risk of CIN compared with other interventions.
Need for RRT	RCT: 1 (72)	High	Direct	NA	Imprecise	Insufficent	Insufficient strength of evidence to support a conclusion
Length of stay	RCT: 1 (72)	High	Direct	NA	Imprecise	Insufficient	Insufficient strength of evidence to support a conclusion

CIN=contrast-induced nephropathy; IOCM=iso-osmolar contrast medium; LOCM= low-osmolar contrast medium; NA=not assessed; NR=not reported RCT=randomized controlled trial; RRT=renal replacement therapy

* Due to heterogeneity in the study limitations across studies, the median study limitation value was chosen when distribution across studies was normal. Where there is a split between study limitation scores, the more conservative study limitation designation was chosen

†Short-term is defined as within 7 days.

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Appendix I. Evidence Tables for Miscellaneous Comparisons

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Abizaid, 1999[1]	Symptomatic coronary artery disease and renal insufficiency (SrCr ≥1.5 mg/dL)	Total		60	NR	NR	NR	NR	NR	NR	
		1	0.45% IV Normal Saline (1 ml/kg/hour) only	20		6(30)	75	NR	NR	NR	
		2	Dopamine (2.5 ug/kg/min) plus 0.45% IV Normal Saline (1 ml/kg/hour)	20		7(35)	74	NR	NR	NR	
		3	Aminophylline (4 mg/kg followed by a drip of 0.4 mg/kg/hour) plus 0.45% IV Normal Saline (1 ml/kg/hour)	20		7(35)	75	NR	NR	NR	
Acikel, 2010[2]	General: excluded CRF	Total		240	48 Hours	NR	59.8 +/- 9.7	NR	NR	NR	
		1	Control	80		29 (36.2)	60.8 +/- 10.8	NR	NR	Current: 30 (37.5)	Excluded CRF
		2	Atorvastatin	80		29 (36.2)	58.7 +/- 8.5	NR	NR	Current: 32 (40)	
		3	Chronic statins	80		30 (37.5)	59.8 +/- 9.6	NR	NR	Current: 32 (40)	
Adolph, 2008[3]	Two Cr concentration levels >106 m mol/l (>1.2mg/dl) within 12 weeks before coronary angiography	Total		145	48 Hours	32(22)	NR	NR	NR	NR	
		1	NaCl + 5% dextrose	74		14(19)	72.7 +/- 6.6	NR	NR	NR	
		2	NaHCO3 + 5% dextrose	71		18(27)	70.1 +/- 8.4	NR	NR	NR	
Alessandri, 2013[4]	Heart Disease, Ischemic heart disease	Total		296	72 Hours	NR	NR	NR	NR	NR	
		1	Sodium Chloride infusion	158		46	64.25	NR	NR	NR	
		2	Sodium Bicarbonate + NAC	138		46	64.25	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Allaqaband, 2002[5]	Creatinine ≥ 1.6 mg/dl	Total		123	48 Hours	52	71	NR	NR	NR	
		1	0.45% Saline	40		16	70	NR	NR	NR	
		2	0.45% Saline + NAC	45		17	70	NR	NR	NR	
		3	0.45% Saline + Fenoldopam	38		19	71	NR	NR	NR	
Aslanger, 2012[6]	STEMI, ST-segment elevation myocardial infarction,	Total		312	72 Hours	NR	NR	NR	NR	NR	
		1	Placebo	99		26(26)	56.1	NR	NR	NR	
		2	IV NAC	108		22(20)	56.1	NR	NR	NR	
		3	IA NAC	105		23(22)	55.9	NR	NR	NR	
Bader, 2004[7]	SCr level between 0.6 and 1.2 Mg/dl	Total		39	48 Hours	NR	NR	NR	NR	NR	
		1	IV Saline infusion before and after procedure	19		3	64	NR	NR	NR	
		2	IV Saline infusion during procedure	20		4	65	NR	NR	NR	
Baskurt, 2009[8]	Moderate degree chronic kidney disease with estimated glomerular filtration rate (eGFR) between 30 and 60 mL min1.73 m2	Total		217	12 Months	87	67.4	NR	NR	NR	
		1	Hydration	72		31	67.1	NR	NR	NR	
		2	Hydration + N-acetylcysteine	73		27	67.9	NR	NR	NR	
		3	Hydration + N-acetylcysteine + theophylline	72		29	67.1	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Brar, 2014[9]	eGFR >60 ml/min/1.73 m^2	Total		396	6 Months	151 (38.1)	71	NR	NR	NR	
		1	IV Normal Saline	200		81 (41)	72	White: 113 (57) Black: 28 (14) Latino: 24 (12) Asian: 29 (15)	NR	NR	
		2	LVEDP-guided IV hydration	196		70 (36)	71	White: 111 (57) Black: 27 (14) Latino: 17 (9) Asian: 28 (14)	NR	NR	
Briguori, 2004[10]	Impairment of renal function: serum creatinine >1.5mg/dl and/or creatinine clearance <60ml/min	Total		192	48 Hours	NR	NR	NR	NR	NR	
		2	NAC + saline	97		13 (13)	68	NR	NR	NR	
		3	Fenoldopam mesylate + saline	95		16 (17)	69	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Briguori, 2004[11]	CKD Cr >1.5 mg/dl and or creatinine clearance <60ml/min	Total		223	48 Hours	NR	NR	NR	NR	NR	
		2	NAC single dose	109		23 (21)	67	NR	NR	NR	
		3	NAC double dose	114		28 (16)	66	NR	NR	NR	
Briguori, 2007[12]	CKD with stable Cr at 2.0 mg/dL and/or estimated glomerular filtration rate 40	Total		326	7 days	NR	NR	NR	NR	NR	
		1	IV Normal Saline + oral NAC	111		21 (19)	71	NR	NR	NR	
		2	IV NaHCO3 + oral NAC	108		13 (12)	70	NR	NR	NR	
		3	IV Normal Saline + IV ascorbic acid + oral NAC	107		27 (21.5)	69	NR	NR	NR	
Briguori, 2011[13]	Estimated glomerular filtration rate (eGFR)	Total		292	7 Days	NR	NR	NR	NR	NR	
		1	IV Sodium bicarbonate + oral NAC	146		43 (29.5)	75	NR	NR	NR	
		2	RenalGuard: IV 0.9% saline + IV NAC + RenalGuard System + IV furosemide	146		58 (39.5)	76	NR	NR	NR	
Chen, 2008[14]	Myocardial Ischemia	Total		936	6 Months	149 (16)	NR	NR	NR	NR	
		1	Normal renal function-Non hydration	330		(15)	60	NR	NR	NR	15% female refers to combined Arms 1 and 2, same with mean age 60
		2	Normal renal function-0.45% saline	330		NR	NR	NR	NR	NR	
		3	Abnormal renal function-NAC + Non hydration	188		(18)	63	NR	NR	NR	18% female refers to combined Arms 3 and 4, same with mean age 63
		4	Abnormal renal function-NAC + 0.45% saline	188		NR	NR	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Cho, 2010[15]	Serum creatinine ≥1.1 mg/dL or CrCl ≤60 mL/min	Total		91	NR	46 (50.5)	78 +/- 8	NR	NR	NR	
		1	IV 0.9% saline	27		(37)	77 +/- 8	NR	NR	Current: 8	
		2	IV sodium bicarb + IV 0.9% saline	21		(47.6)	78 +/- 9	NR	NR	Current: 9	
		3	Oral fluids (water)	22		(55)	81 +/- 7	NR	NR	Current: 9	
		4	Oral fluids (water) + oral bicarb	21		(62)	79 +/- 2	NR	NR	Current: 7	
Demir, 2008[16]	Patients with renal insufficiency	Total		97	3 Days	43 (44)	NR	NR	NR	NR	
		1	Saline	20		5 (25)	58.2 +/- 11.3	NR	NR	NR	
		2	NAC + control (NAC)	20		9 (45)	62.0 +/- 15.8	NR	NR	NR	
		3	Misoprostol + control (M)	20		11 (55)	56.5 +/- 13.0	NR	NR	NR	
		4	Theophylline + control (T)	20		9 (45)	56.3 +/- 13.0	NR	NR	NR	
		5	Nifedipine + control (N)	17		9 (53)	60.1 +/- 10.7	NR	NR	NR	
Erol, 2013[17]	serum creatinine >1.1mg/dl, cardiac catheterization/intervention	Total		159	96 Hours	NR	NR	NR	NR	NR	
		1	Saline hydration	80		54 (68)	65	NR	NR	Current: 21 (25)	
		2	Saline hydration + allopurinol	79		61 (77.5)	65	NR	NR	Current: 20 (25)	
Firouzi, 2012[18]	Non-emergent coronary angiography with creatinine < 2.0 mg/dl	Total		286	48 Hours	NR	NR	NR	NR	Current: 31 (21.23)	
Firouzi, 2012[18] (continued)		1	Control	146		(30.83)	57.9 (SD 10.16)	NR	NR	Current: 31 (21.23)	
		2	Pentoxifylline	140		(23.58)	56.8 (SD 10.69)	NR	NR	Current: 41 (29.28)	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Frank, 2003[19]	Patients with a known chronic renal insufficiency, not yet dialysis dependent	Total		17	NR	NR	NR	NR	NR	NR	
		1	0.9% saline volume expansion	10		1	57.6+/-12.4	NR	NR	NR	
		2	0.9% saline volume expansion + high-flux HD	7		2	66.8+/-9.2	NR	NR	NR	
Gu, 2013[20]	General	Total		859	NR	239 (27.8)	NR	Other: 859 (100)	NR	NR	
		1	Control--saline	437		110 (25.2)	59.0 +/- 14	NR	NR	NR	
		2	Furosemide	422		129 (30.6)	58.0 +/- 14	NR	NR	NR	
Gunebakmaz, 2012[21]	Coronary angiography with creatinine ≥ 1.2 mg/dl	Total		120	5 Days	NR	NR	NR	NR	NR	
		1	Saline	40		15	66.4 +/- 10.7	NR	NR	NR	
		2	Saline + Nebivolol	40		11	64.1+/- 9	NR	NR	NR	
		3	Saline + NAC	40		11	64.7 +/- 11.9	NR	NR	NR	
Hafiz, 2012[22]	Serum creatinine >1.6 mg/dl in non-diabetics and >1.4 mg/dl in diabetics or an estimated glomerular filtration rate (eGFR) of <50 ml/min/1.73 m2	Total		320	48 Hours	138 (43.1)	Median: 73;Range: 63-80	Black: 151 (47.2)	NR	NR	
		2	Normal Saline with or without NAC	161		69 (42.9)	Median: 73;Range: 63-80	Black: 80(49.7)	NR	NR	
		3	Sodium Bicarbonate with or without NAC	159		69 (43.4)	Median: 74;Range: 65-80	Black: 71(44.7)	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Hans, 1998[23]	Defined as SrCr of at least 1.4 mg/dL (of note, the abstract mentions the range of 1.4 to 3.5 mg/dL, but the actual inclusion seemed to be based on the SrCr of at least 1.4 mg/dL)	Total		55	4 Days	NR	NR	NR	NR	NR	
		1	Placebo	27		3	71	NR	NR	NR	
		2	Dopamine	28		3	75	NR	NR	NR	
Hashemi, 2005[24]	General	Total		88	48 Hours	NR	NR	NR	NR	NR	
		1	Placebo	46		13 (28)	55.1	NR	NR	NR	
		2	Captopril	42		12 (29)	55.1	NR	NR	NR	
Heguilen, 2013[25]	General	Total		0	3 Days	NR	NR	NR	NR	NR	
		2	NaHCO3 + dextrose	47		15	67.7	NR	NR	NR	
		3	NaHCO3 + NAC +dextrose	44		11	64.8	NR	NR	NR	
		4	NaCl + NAC+dextrose	42		8	69.3	NR	NR	NR	
Holscher, 2008[26]	General	Total		412	30 Days	NR	NR	NR	NR	NR	
		1	Hydration only	139		68 (16.5)	67.1	NR	NR	NR	
		2	Hydration plus dialysis	134		58 (15.5)	66.8	NR	NR	NR	
		3	Hydration plus NAC	139		10 (26.3)	70.5	NR	NR	NR	
Huber, 2006[27]	General	Total		91	48 Hours	31	58.5+/-14.8;Range: 21-89	NR	NR	NR	
		2	Theophylline	NR		NR	59.6	NR	NR	NR	
		3	Acetylcysteine	NR		NR	55.4	NR	NR	NR	
		4	Theophylline + Acetylcysteine	NR		NR	60.6	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Kimmel, 2008[28]	Mild to moderately impaired kidney function: serum creatinine ≥ 1.2 mg/dl or a creatinine clearance < 50 ml/min	Total		54	2 Days	NR	NR	NR	NR	NR	
		1	Placebo	17		(30)	66.8	NR	NR	NR	
		2	NAC	19		(21)	71.5	NR	NR	NR	
		3	Zinc	18		(28)	67.2	NR	NR	NR	
Kinbara, 2010[29]	Stable coronary artery disease	Total		45	48 Hours	NR	NR	NR	NR	NR	
		1	Hydration	15		6 (40)	70	NR	NR	NR	
		2	Hydration and aminophylline	15		5 (33)	71	NR	NR	NR	
		3	Hydration and N-acetylcysteine	15		6 (40)	70	NR	NR	NR	
Klima, 2012[30]	>93 umol/L for women and >117 umol/L for men or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2	Total		258	48 Hours	92(36)	77;Range: 69-81	NR	NR	NR	
		1	0.9% saline	89		39(38)	75;Range: 70-82	NR	NR	NR	
		2	Long term sodium bicarbonate	87		30(34)	78;Range: 70-82	NR	NR	NR	
		3	Short term sodium bicarbonate	82		28(34)	75;Range: 65-81	NR	NR	NR	
Koc, 2012[31]	Serum creatinine (SCr) ≥ 1.1 mg/dL or creatinine clearance ≤ 60 mL/mi	Total		220	48 Hours	NR	NR	NR	NR	NR	
		1	IV 0.9% saline	60		14(23)	64	NR	NR	Current: 17(28)	
		2	IV NAC plus high-dose IV 0.9% saline	80		19(24)	62	NR	NR	Current: 13(17)	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Koc, 2012[31] (continued)		3	High-dose IV 0.9% saline	80		17 (21)	65	NR	NR	Current: 15 (19)	
Kong, 2012[32]	Coronary artery disease	Total		120	6.1 Months	NR	NR	NR	NR	NR	
		1	IV 0.9% saline	40		18 (45)	55.7 ± 11.9	NR	NR	NR	
		2	Oral hydration before and after procedure	40		19 (47)	57.2 ± 9.2	NR	NR	NR	
		3	Oral hydration after procedure	40		16 (40)	54.9 ± 10.8	NR	NR	NR	
Kooiman, 2014[33]	CKD (eGFR < 60 mL/min/1.73m^2)	Total		138	2 Months	69 (50.0)	NR	NR	NR	NR	
		1	No hydration	67		32 (47.8)	70	NR	NR	NR	
		2	IV 1.4% $NaHCO_3$	71		37 (52.1)	71	NR	NR	NR	
Kotlyar, 2005[34]	Serum creatinine concentrations ≥0.13 mmol/l	Total		60	30 Days	NR	NR	NR	NR	NR	
		1	IV hydration	19		2 (10)	69	NR	NR	NR	
		2	NAC 300mg	20		5 (25)	66	NR	NR	NR	
		3	NAC 600mg	21		3 (14)	67	NR	NR	NR	
Krasuski, 2003[35]	Moderate renal insufficiency with serum creatinine from 1.6mg/dl to 3mg/dL	Total		0	48 Hours	NR	NR	NR	NR	NR	
		1	overnight hydration dextrose plus saline	26		(27)	69	NR	NR	NR	
		2	Bolus normal saline	37		(11)	68	NR	NR	NR	
Kumar, 2014[36]	Coronary block	Total		275	5 days	110 (22)	65	NR	NR	NR	
		1	IV NS	90	NR	NR	NR	NR	NR	NR	
		2	Oral NAC + IV NS	90	NR	NR	NR	NR	NR	NR	
		3	Allpurinol + IV NS	95	NR	NR	NR	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Lawlor, 2007[37]	Preexisting renal impairment. Stable , chronic renal insufficiency	Total		78	48 Hours	NR	NR	NR	NR	NR	
		1	IV Hydration	25		8 (32)	NR	NR	NR	Current: 6 (24)	
		2	IV Hydration + oral NAC	25		6 (24)	NR	NR	NR	Current: 19 (76)	
		3	Oral Hydration + oral NAC	28		10 (36)	NR	NR	NR	Current: 8 (28)	
Li, 2009[38]	Planned coronary angiography	Total		205	3 Days	NR	NR	NR	NR	NR	+/- SD
		1	Control	103		37	63 +/- 11	NR	NR	NR	
		2	Probucol	102		52	62 +/- 11	NR	NR	NR	
Li, 2011[39]	Mild and/or moderate renal insufficiency: ≥60 to ≤89 ml·min^-1·1.73 m^-2 and ≥30 to ≤59 ml·min^-1·1.73 m^-2 in eGFR	Total		114	72 Hours	NR	NR	NR	NR	NR	
		1	Control	62		27 (44)	61.8 +/- 9.4	NR	NR	NR	
		2	Benazepril	52		22 (42)	60.7 +/- 9.2	NR	NR	NR	
Li, 2014 [40]	CIN Risk Score >11	Total		163	3 Days	54 (33.1)	65.4	NR	NR	NR	
		1	IV Normal Saline	81		29 (35.8)	63.6	NR	NR	NR	
		2	IV Prostaglandin E1	82		25 (30.5)	64.7	NR	NR	NR	
Liu, 2013[41]	Mild to moderate kidney disease (eGFR 60-89 ml/min/1.73 m2)	Total		156		62 (39.7)	NR	NR	NR	NR	
		1	Statin	80	6 Months	31 (38.7)	65.4	NR	NR	NR	
		2	Statin plus alprostadil	76		31 (40.8)	66.3	NR	NR	NR	
Ludwig, 2011[42]	Chronic renal impairment	Total		100	48 Hours	NR	NR	NR	NR	NR	
		1	Control	51		9 (19)	68	NR	NR	NR	
		2	MESNA	49		15 (29)	68	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Maioli, 2008[43]	Patients with chronic kidney dysfunction undergoing planned coronary angiography or intervention	Total		502	10 Days	NR	NR	NR	NR	NR	
		2	IV Isotonic Saline plus oral NAC	252		99 (39)	Median, 74 ; Range, 70-79	NR	NR	NR	
		3	IV Sodium Bicarbonate plus oral NAC	250		107 (43)	Median, 74 ; Range, 67-79	NR	NR	NR	
Maioli, 2011[44]	STEMI, ST-segment elevation-myocardial infarction	Total		0	3 Days	NR	NR	NR	NR	NR	
		1	No hydration	150		40 (26.6)	64	NR	NR	NR	
		2	Late IV 0.9% saline	150		41 (27.3)	66	NR	NR	NR	
		3	Early IV sodium bicarbonate	150		35 (23.3)	65	NR	NR	NR	
Manari, 2014[45]	Cardiovascular: STEMI meeting inclusion criteria	Total		592	72 hours CIN; 1 year for death outcomes	149 (25.2)	NR	NR	NR	NR	
		1	IV normal saline	151		38 (25.1)	65	NR	NR	Current: 47 (37)	
		2	High-dose infusion of IV normal saline	142		32 (22.5)	65.2	NR	NR	Current: 44 (31)	
		3	IV standard bicarbonate	145		41 (28.5)	63.9	NR	NR	Current: 49 (34)	
		4	High-dose IV bicarbonate	154		38 (24.7)	65.2	NR	NR	Current: 44 (29)	
Marenzi, 2006[46]	Acute MI, ST segment elevation acute MI	Total		354	NR	NR	NR	NR	NR	NR	
		1	Placebo	119		22 (18)	62.5	NR	NR	Current: 60 (50)	
		2	Standard dose NAC	115		28 (24)	62.5	NR	NR	Current: 57 (50)	
		3	High dose NAC	118		18 (15)	62.2	NR	NR	Current: 77 (65)	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Marenzi, 2012[47]	CKD-eGFR <60 ml/min/1.73 m 2 ,General	Total		170	72 Hours	NR	NR	NR	NR	NR	
		1	Saline Hydration	83		18 (22)	73 +/- 7	NR	NR	Current: 7 (13)	
		2	Furosemide plus matched hydration	87		19 (22)	73 +/- 7	NR	NR	Current: 4 (7)	
Marron, 2007[48]		Total		NR	48 Hours		NR	NR	NR	NR	
		1	Isotonic 0.9% saline	36		10	64	NR	NR	NR	
		2	Hypotonic 0.45% saline	35		13	68	NR	NR	NR	
Mueller, 2002[49]	General	Total		1383	30 Days	NR	NR	NR	NR	NR	
		1	Isotonic Saline hydration	685		178 (26)	64	NR	NR	NR	
		2	.45% sodium chloride plus 5% glucose	698		176 (25)	64	NR	NR	NR	
Ng, 2006[50]	Stable renal disease Cr >1.2	Total		95	72 Hours	(24.8)	68 +/- 10	NR	NR	NR	
		2	NAC	48		(18.8)	67 +/- 10	NR	NR	NR	
		3	Fenoldopam	47		(29.8)	69 +/- 11	NR	NR	NR	
Oguzhan, 2013[51]	Coronary angiography with serum creatinine <2.1 mg/dl	Total		90	NR	NR	NR	NR	NR	NR	
		2	AVH (amlodipine valsartan hydration group)	45		(40)	66.38	NR	NR	Ever: (48.9)	
		3	H (hydration group)	45		(33.3)	62.07	NR	NR	Ever: (53.3)	
Ozhan, 2010[52]	General	Total		130	48 Hours	53	54 +/- 10	NR	NR	NR	
		2	NAC	70		30	55 +/- 8	NR	NR	NR	
		3	NAC + Atorvastatin	60		23	54 +/- 10	NR	NR	NR	
Pakfetrat, 2009[53]	General	Total		286	48 Hours	111 (39)	57.9	NR	NR	NR	
		1	sodium chloride	96		34 (35)	58.5	NR	NR	NR	
		2	sodium bicarbonate in dextrose solution	96		40 (42)	57.8	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Pakfetrat, 2009[53] (continued)		3	sodium chloride plus oral Acetazolamide	94		47 (50)	57.5	NR	NR	NR	
Ratcliffe, 2009[54]	Renal insufficients, Cr Men >132.6 mg/dL Women >114.9 mg/dL and/or diabetics	Total		78	7 Days	32 (40)	66	White: (13) Black: (33) Latino: (36) Asian/Pac: (19)	NR	NR	
		1	IV normal saline	15		6 (40)	64	White: (20) Black: (27) Latino: (33) Asian/Pac: (20)	NR	NR	
		2	IV normal saline + IV/oral NAC	21		10 (48)	65	White: (10) Black: (33) Latino: (33) Asian/Pac: (24)	NR	NR	
		3	IV NaHCO3	19		8 (42)	67	White: (6) Black: (44) Latino: (33) Asian/Pac: (17)	NR	NR	
		4	IV NaHCO3+ IV/oral NAC	23		7 (30)	65	White: (14) Black: (29) Latino: (43) Asian/Pac: (14)	NR	NR	
Recio-Mayoral, 2007[55]	Acute coronary Syndrome, acute coronary syndrome (ACS) patients who were admitted coronary care unit	Total		111	7 Days	NR	NR	NR	NR	NR	
		1	Saline + NAC after procedure	56		16 (29)	64	NR	NR	NR	
		2	IV Bolus+ NAC before procedure +NAC after procedure	55		18 (32)	65	NR	NR	NR	
Reinecke, 2007[56]	General	Total		424	Median 553 Days	NR	NR	NR	NR	NR	
		1	Hydration only	140		24 (17.1)	67.9	NR	NR	Ever: 80 (57.1)	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Reinecke, 2007[56] (continued)		2	Hydration + Dialysis	138		24 (17.4)	67.9	NR	NR	Ever: 74 (53.6)	
		3	Hydration + NAC	146		25 (17.1)	66.7	NR	NR	Ever: 75 (51.4)	
Rosenstock, 2008[57]	Chronic kidney disease (CKD) stages 3–4 (glomerular filtration rate 15–60 ml/min/1.73 m2	Total		283	72 Hours	NR	NR	NR	NR	NR	
		1	Naive to angiotensin blockade	63		23 (37)	71.8	NR	NR	Current: 15 (24)	
		2	Continue angiotensin blockade during and after procedure	113		52 (46)	71.8	NR	NR	Current: 25 (22)	
		3	Discontinue angiotensin blockade morning of procedure and 2hrs after procedure	107		41 (38)	71.8	NR	NR	Current: 24 (22)	
Schmidt, 2007[58]	General	Total		96	NR	NR	NR	NR	NR	NR	
		2	NAC plus sodium bicarbonate	47		14 (42)	67	NR	NR	NR	
		3	NAC plus standard hydration	49		11 (29)	68.3	NR	NR	NR	
Shehata, 2014[59]	Diabetic and mild to moderate CKD (eGFR 30-90 ml/min/1.73 m^2)	Total		100	10 Days	68 (68)	59	NR	NR	NR	
		2	IV Normal Saline + Oral NAC	50		17 (34)	59	NR	NR	Current: 34 (68)	
		3	IV Normal Saline + Oral NAC + Oral Trimetazidine	50		15 (30)	58	NR	NR	Current: 35 (70)	
Solomon, 1994[60]	Cr >1.6mg/dl - CrCl <60	Total		78	24 Hours	NR	NR	NR	NR	NR	
		1	Saline	28		5	67 +/- 11	NR	NR	NR	
		2	Mannitol + Saline	25		6	60 +/- 13	NR	NR	NR	
		3	Furosemide + Saline	25		13	63 +/- 13	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Stevens, 1999[61]	Baseline serum creatinine greater than 1.8 mg/dl	Total		98	48 Hours	NR	NR	NR	NR	NR	
		1	IVF alone	55		21	69.6	NR	NR	NR	
		2	IVF + Furosemide + Dopamine + Mannitol	22		5	72.3	NR	NR	NR	
		3	IVF + Furosemide + Dopamine	21		6	67.0	NR	NR	NR	
Tamura, 2009	General	Total		144	7 Days	NR	NR	NR	NR	NR	
		1	Normal saline	72		12 (16.7)	NR	NR	NR	NR	
		2	Normal Saline + NaHCO3	72		5.98 (.83)	NR	NR	NR	NR	
Talati, 2012[62]	Coronary procedures	Total		104	72 Hours	NR	NR	NR	NR	NR	
		1	No Fenoldapam	52		17 (33)	69.4	NR	NR	NR	
		2	Fenoldopam	52		13 (25)	69.4	NR	NR	NR	
Trivedi, 2003[63]	Coronary artery disease	Total		53	48 Hours	NR	NR	NR	NR	NR	
		1	Oral hydration	26		0 (0)	67.2 +/- 11.2	NR	NR	NR	
		2	IV Hydration (0.9% saline)	27		1 (3.8)	68.5 +/- 8	NR	NR	NR	
Weisberg, 1994[64]	Stable plasma creatinine concentration greater or equal to 1.8 mg/dL	Total		26	:	NR	NR	NR	NR	NR	
		1	Saline	8		NR	NR	NR	NR	NR	
		2	Dopamine	8		NR	NR	NR	NR	NR	
		3	ANP	4		NR	NR	NR	NR	NR	
		4	Mannitol	6		NR	NR	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Wolak, 2013[65]	General	Total		94	48 Hours	32 (34.0)	65	NR	NR	NR	
		1	Continued ACE/ARB	33		15 (45.5)	67.6	NR	NR	Current: 4 (12.1) Former: 5 (15.2)	
		2	Short delay of ACE/ARB	30		7 (25.8)	64.8	NR	NR	Current: 8 (25.8) Former: 12 (38.7)	
		3	Long delay of ACE/ARB	31		10 (30.0)	61.0	NR	NR	Current: 7 (24.1) Former: 8 (27.6)	
Xinwei, 2009[66]	Acute Coronary syndrome: ACS was defined as any one of the following: (1) unstable angina pectoris; (2) ST-segment elevation myocardial infarction; and (3) non–ST-segment elevation myocardial infarction	Total		228	48 Hours	NR	NR	NR	NR	NR	
		2	Simvastatin 20	115		67 (58)	NR	NR	NR	NR	
		3	Simvastatin 80	113		79 (70)	NR	NR	NR	NR	
Yavari, 2014[67]	baseline serum creatinine ≤132.6 mol/l (1.5 mg/dl)	Total		199	48 Hours	NR	NR	NR	NR	NR	
		1	0.9% IV Normal Saline	102		NR	53.7	NR	NR	NR	
		2	0.9% IV Normal Saline + Oral Pentoxifyllline	97		NR	54.4	NR	NR	NR	

Evidence Table I-1. Participant Characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, year	Study Population	Arm*	ARM define	N	Follow-up Period	Sex, N female (%)	Age, mean unless otherwise specified	Race	Education	Smoking status	Comments
Yin, 2013[68]	Coronary Care Unit, acute STEMI and acute (NSTEMI) requiring urgent coronary intervention due to ongoing ischemic symptoms	Total		204	3 Days	NR	NR	NR	NR	NR	
		1	No probucol	108		34 (31.5)	Median: 12.5;Range: 65.1	NR	NR	NR	
		2	Probucol	96		29 (30.2)	65.1;Range: 10.5	NR	NR	NR	

ACS=Acute Coronary Syndrome, AVH= amlodipine valsartan hydration group, CCS=Canadian Cardiovascular Society, CHF=Chronic Heart Failure, CIN=Contrast Induced Nephropathy, CKD=Chronic Kidney Disease, CK-MB=Creatine Kinase MB, CPK=Creatine Phosphokinase, Cr=Creatinine, CrCl=Creatinine Clearance, CRF=Chronic Renal Failure, eGFR=Estimated Glomerular Filtration Rate, GFR=Glomerular Filtration Rate, H=hydration group, HD=Hemodialysis, ICU=Intensive Care Unit, IU=International Units, IV=Intravenous, IVF=Intravenous Fluid, Mg/dl=milligram per deciliter, Mg/kg/hour=Milligram per kilogram per hour, Mg/kg=milligram per kilogram, MI=Myocardial Infarction, ml/min/1.73m^2=milliliter per minute per 1.73 meter squared, Ml/min=milliliter per minute, Mmol/l=millimole per liter, N=Sample Size, NAC=N-acetylcysteine, NR=Not Reported, NSTEMI=non-ST-segment elevation-mycordial infarction, OHT=Orthotopic Heart Transplantation, PCI=Percutaneous Coronary Intervention, SCr=Serum Creatinine, SD=Standard Deviation, SrCr=Serum Creatinine, STEMI= ST-segment elevation-mycordial infarction, UA=Unstalbe Angina, Ug/kg/min=microgram per kilogram per minute, Umol/l=micromole per liter

* if there is no "Arm 1" there is no control group.

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Abizaid, 1999[1]	2	RCT/ Controlled	No	NR	NR	Single-center	Serum creatinine ≥1.5 mg/dl. No preexisting ARF, not on chronic dialysis, No electrocardiographic or enzymatic evidence of acute myocardial infarction, left ventricular ejection fraction >20%, No allergy to contrast medium, and No pregnancy.	
Acikel, 2010[2]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	coronary angiography; GRF > 60 ml/min; a low-density lipoprotein (LDL) level of more than 70 mg/dl and receiving no cholesterol-lowering medication	
Adolph, 2008[3]	2	RCT/ Controlled	No	NR	NR	Single-center	>18 years, serum creatinine > 106umol/l (1.2 mg/dl) and/or eGFR of 63 ml/min/1.73 m2, No Acute myocardial infarction requiring primary or rescue coronary intervention, allergies to trial medication, exposure to contrast medium within the preceding 7 days, thyroid dysfunction, pregnancy, uncontrolled hypertension (systolic blood pressure >180mmHg or diastolic blood pressure >100mmHg), life-limiting concomitant disease, pulmonary edema, chronic dialysis, and administration of dopamine, manitol, fenoldopam, or N-acetylcysteine..	
Allaqaband, 2002[5]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	NR	scheduled to undergo cardiovascular intervention with radio contrast agent; creatinine of more than 1.6 mg/dl or an estimated creatinine clearance of less than 60 ml/min	
Aslanger, 2012[6]	2	RCT/ Controlled	No	2007 to 2009	NR	Single-center	>30years, Primary angioplasty, Other Risk factors, ST-segment elevation myocardial infarction, angioplasty within 12 hours of symptoms No allergies to NAC Not on dialysis	
Bader,2004[7]	2	RCT/ Controlled	No	NR	NR	NR	Computer tomography (CT) or digital subtraction angiography (DSA); no pregnancy, no uncontrolled arterial hypertension, no severe heart failure (NYHA II – IV), no liver failure and no nephrotic syndrome. Serum creatinine levels 0.6-1.2 mg/dl. Stable serum creatinine concentrations only were included	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Baskurt, 2009[8]	2	RCT/ Controlled	No	2008 to 2010	NR	Multi-center	>70year, coronary or peripheral arterial diagnostic intra- vascular angiography or percutaneous intervention chronic renal failure (stable serum creatinine concentrations >132.6 umol/L, at least 1 risk factor for contrast-induced acute kidney injury: age > 70 years, chronic renal failure (stable serum creatinine concentrations > 132.6 mol/L [1.5 mg/dL]), diabetes mellitus, clinical evidence of congestive heart failure, left ventricular ejection fraction < 0.45, or hypotension. no patient on dialysis and those with ST-segment elevation myocardial infarction undergoing primary angioplasty, no woman pregnant, breastfeeding, or aged 45years and not using contraceptive methods	
Brar, 2014[9]	2	RCT/ Controlled	No	2010-2012	Other: Cardiac catheter laboratory	Single-center	>18 years; requires a cardiac catheterization; eGFR >60 ml/min/1.73 m^2; Ability to obtain consent from participants; no emergency cardiac catheterisation (eg. primary percutaneous coronary intervention for ST-segment elevation myocardial infarction); no renal replacement therapy; no exposure to radiographic contrast media within the previous 2 days; no allergy to radiographic contrast media; no acute decompensated heart failure; no severe valvular heart disease; no mechanical aortic prosthesis; no left ventricular thrombus; no history of kidney or heart transplantation; no change in estimated GFR of 7.5% or more per day or a cumulative change of 15% or more during the pre ceding 2 or more days. Must have either: diabetes mellitus, congestive heart failure, hypertension or older than 75 years.	
Briguori, 2004[11]	2	RCT/ Controlled	No	2009 to 2010	NR	NR	>19years, coronary angiography and/or percutaneous coronary intervention; Impaired renal function; creatinine clearance (CrCl) <60 ml/min, no pregnancy, no lactation, not received contrast media <7 days before the procedure, no emergent CAG in which sufficient pre-procedural hydration was unavailable, no acute renal failure, no end-stage renal disease requiring dialysis, no history of hypersensitivity reaction to contrast media, no cardiogenic shock, no pulmonary edema, and no mechanical ventilator support	
Briguori, 2004[10]	2	RCT/ Controlled	No	2003 to 2003	NR	Single-center	Scheduled for coronary or peripheral angiography/angioplasty,; serum creatinine >1.5mg/dl and/or creatinine clearance <60ml/min	
Brigouri, 2007[12]	2	RCT/ Controlled	No	2005 to 2006	NR	NR	>18 years, stable serum creatinine concentration >2.0mg/dl and/or eGFR <40ml/min/1.73m^2. No serum creatinine 8mg/dl, history of dialysis, multiple myeloma, pulmonary edema, ami, recent exposure to contrast (2 days of study), pregnancy, or had administration of theophylline, dopamine, mannitol or fenoldopam.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Briguori, 2011[13]	2	RCT/ Controlled	Yes	2009 to 2010	NR	Multi-center	Scheduled for coronary/peripheral angiography or angioplasty, estimated glomerular filtration rate (eGFR), with chronic kidney disease, No presence of: AMI, acute pulmonary edema, cardiogenic shock, dialysis, multiple myeloma, sodium bicarbonate, theophyline, dopamine, mannitol or fenoldopam 48 hours before procedure, no recent administration of iodinated contrast media, no current enrollment in any other study.	
Mueller, 2002[49]	2	RCT/ Controlled	No	1998 to 1999	NR	NR	Elective or emergency angioplasty; no end-stage renal failure with regular hemodialysis, no cardiogenic shock, and no mechanical ventilation,	
Chen, 2008[14]	2	RCT/ Controlled	No	2004 to 2006	Inpatient (including ICU)	Multi-center	Percutaneous coronary intervention, the coronary anatomy suitable for PCI, no emergency coronary artery bypass grafting (CABG) being required, no patients in chronic peritoneal or hemodialysis treatment, no acute myocardial infarction (AMI) at admission. Myocardial ischemia.	
Cho, 2010[15]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	>18years, CAG, SCr >=1.1mg/dl, no serum creatinine levels greater than 8.0 mg/dL, no change in serum creatinine levels of at least 0.5 mg/dL during the previous 24 hours, no preexisting dialysis, no multiple myeloma or other myeloproliferative disease, no current decompensated heart failure or significant change in base- line New York Heart Association Class, no current myocardial infarction, no symptomatic hypokalemia, uncontrolled hypertension (treated systolic blood pressure > 200 mmHg or diastolic blood pressure > 100 mmHg), no exposure to radio contrast within 7 days of enrollment into this study, no emergency catheterization, no allergy to radiographic contrast, no pregnancy, administration of dopamine, no mannitol, fenoldapam, or NAC during the time of the study, no exacerbation of chronic obstructive pulmonary disease, no serum bicarbonate greater than 28 mEq/L, and sodium less than 133 mEq/L.	
Demir, 2008[16]	1	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	CT, No diabetes, no chronic renal failure, no uncontrolled hypertension or hypotension, no pregnancy, no ESRD, no renal transplantation, no dialysis history, no sensitivity to CM, no nephrotoxic drug use (NSAIDs, aminoglycoside, etc)	
Durham, 2002[69]	2	RCT/ Controlled	No	NR	NR	Multi-center	>18years, coronary angiography and/or PCI, mild to moderate renal dysfunction with serum creatinine (SCr) ≥ 1.1 mg/dL or creatinine clearance ≤ 60 mL/min, Does not have contrast-agent hypersensitivity, pregnancy-lactation, decompensated heart failure, pulmonary edema, emergency catheterization, acute renal failure or end-stage renal failure.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Erol, 2013[17]	2	RCT/ Controlled	No	2004 to 2006	NR	Single-center	Undergoing cardiac catheterization; serum creatinine >1.1mg/dl, no acute myocardial infarction requiring primary/rescue coronary intervention within 24 hours. No cardiogenic shock, acute renal failure, peritoneal dialysis/hemodialysis, planned post contrast dialysis, or history of intravascular administration of contrast agents or anticipated re-administration of contrast agents within the following 4-days.	
Firouzi, 2012[18]	2	RCT/ Controlled	No	NR	NR	Single-center	Undergoing primary PCI, CVD; acute myocardial infarction; Patients with AMI undergoing primary PCI were eligible if their symptoms lasted 12 h and if they had ST-segment elevation of 0.1 mV in 2 extremity leads or 0.2 mV in 2 pre-cordial leads. No previous fibrinolysis in < 12 hours, known N-acetylcysteine allergy, chronic dialysis, and pregnancy. No contraindications to magnetic resonance imaging (MRI)	
Frank, 2003[19]	2	RCT/ Controlled trial	No	2000 to 2001	Inpatient (including ICU)	Single-center	>18; coronary angiography; not requiring HD; Stable SrCr (> 3mg/dl); no allergy to contrast medium; not pregnant; no acute renal failure	
Gu, 2013[20]	2	RCT/ Controlled	No	2009 to 2011	Inpatient (including ICU)	Single-center	Coronary angiography or percutaneous coronary intervention; New York Heart Association stage < 4; no other serious illness that is inappropriate for hydration.	
Gunebakmaz, 2012[21]	2	RCT/ Controlled trial	No	2008 to 2009	NR	Single-center	Coronary angiography or ventriculography; , excluded Baseline Creatinine > 1.2 mg/dl	
Hafiz, 2012[22]	2	RCT/ Controlled	No	2004 to 2006	NR	Multi-center	>18, undergoing coronary and peripheral angiogram, serum creatinine >1.6 mg/dl in non-diabetics and >1.4 mg/dl in diabetics or an estimated glomerular filtration rate (eGFR) of <50 ml/min/1.73 m^2 Not on dialysis. Stable renal function (defined as no change in serum creatinine of >0.4 mg/dl within 48 hours prior to the index procedure. No pulmonary edema, no serum bicarbonate level >34 mmol/L. Have not received fenoldopam, mannitol, dopamine, or NAC within 48 hr prior to the index procedure. Was not in cardiogenic shock. No allergies to contrast media, not pregnant, and able to provide informed consent	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Hans, 1998[23]	2	RCT/ Controlled	No	1989 to 1994	NR	NR	Arteriography of the abdominal and lower extremity arteries by catheter techniques; Serum creatinine greater than or equal to 1.4mg/dl, Other Risk factors, peripheral arterial occlusive disease (see #16 for explanation), Patients not taking aminoglycosides or not undergoing combined studies (such as carotid and lower extremity arteriograms) [The Methods section mentions that all patients had disabling claudication or lower extremity ischemia, but those were not specified as inclusion criteria per se. This would probably be more a result than something in the Methods section, but because it is listed there, it will be added here. It is most likely something that is a finding based on the patient population that would undergo the imaging that was used. The text also mentions that they selected patients who underwent the imaging test described because of peripheral arterial occlusive disease, so the latter is being added as an inclusion criterion]	
Hashemi, 2005[24]	2	RCT/ Controlled	No	2004 to 2004	NR	Single-center	Undergoing coronary angiography, Contrast used for each patient 100-300mls. No calcium antagonists, ACE-I, or theophylline prescribed within 2 days before procedure. Baseline creatinine below 2 mg/dl	
Heguilen, 2013[25]	1,2	RCT/ Controlled	No	NR	NR	Single-center	> 18years, scheduled for cardiac catheterization or arteriographic procedure, Stable serum creatinine >1.25 mg/dL or Cockcroft-Gault-estimated creatinine clearance <45 ml/min non-emergency catheterization; without pulmonary edema; no preexisting dialysis; non recent exposure to CM; no history of multiple myeloma; controlled hypertensives; without hemodynamic instability; not being treated with the following medications: dopamine, mannitol, fenoldopam, aminophylline, theophylline ascorbic acid or NAC; Non pregnant or childbearing women; or not hypersensitive to CM or NAC. The SCr shouldn't be [4.5 mg/dl ([364.5 lmol/l) or no change in SCr of at least 0.5 mg/dl (44.2 lmol/l) within the previous week.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Holscher, 2008[26]	2	RCT/ Controlled	No	NR	NR	Single-center	>14 years and <79years, coronary angio-PCA- CT scan-IV pyelography; No acute renal failure, maintenance dialysis, history of acute myocardial infarction, left ventricular ejection fraction (EF) ≤ 25%, allergy to contrast media, pregnancy, contraindications for theophylline use such as untreated high-grade arrhythmia or history of seizure, or use of acetylcysteine.	excluded HD and ARF
Huber, 2006[27]	1,2	RCT/ Controlled	No	2006 to 2008	NR	Single-center	Elective coronary Angiography; no hemodialysis creatinine clearance <60ml/min, No treatment with a statin, contraindication to statin treatment, previous contrast media administration (within 10 days of study entry), end-stage renal failure requiring dialysis, or informed refusal of consent	
Kimmel, 2008[28]	2	RCT/ Controlled	No	2005 to 2006	NR	Single-center	>18years, coronary angiography with or without PCI, not on dialysis; no acute renal failure or ESRD, no participation in an investigational drug or device trial within 30 days; not having received CM within 7 days of study entry; not scheduled major surgical intervention; no history of hypersensitivity reaction to iodinated CM; unstable hemodynamic conditions; use of N-acetylcysteine (NAC), metformin, or non-steroidal anti-inflammatory drugs within 48 hour to the procedure; intravenous use of diuretics or mannitol; and pregnancy or lactation. CrCl <60ml/min	
Kinbara, 2010[29]	2	RCT/ Controlled trial	No	2006 to 2007	Inpatient (including ICU)	Single-center	Coronary angiography; Other Risk factors, Stable coronary artery disease; Exclusion criteria of this study included acute myocardial infarction requiring primary or rescue PCI, use of vasopressors before PCI, cardiogenic shock, current peritoneal dialysis or hemodialysis, planned post-contrast dialysis, or allergies to the medications being studied	
Klima, 2012[30]	1,2	RCT/ Controlled	No	2005 to 2009	NR	Multi-center	>18 years, undergoing IA or IV radiocontrast procedure within 24 hours, 93 mmol/L for women and .117 mmol/L for men or estimated glomerular filtration rate (eGFR) ,60 mL/min/1.73 m2, No pre-existing dialysis, no allergies to radiographic contrast, not pregnant, no severe heart failure, no NAC 24 hours before contrast procedure, no clinical condition requiring continuous fluid therapy	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Koc, 2012[31]	2	RCT/ Controlled	Yes	NR	NR	NR	Patients who were ≥18 years of age, with a creatinine clearance (CrCl)≤60mL/min and/or baseline serum creatinine level (SCr)≥1.1 mg/dL. No contrast-agent hypersensitivity, pregnancy-lactation, decompensated heart failure, pulmonary edema, emergency catheterization, acute renal failure and end-stage renal failure.	
Kong, 2012[32]	2	RCT/ Controlled	No	2010 to 2010	NR	NR	Coronary angiography or PCI; no renal dysfunction, No definitive or suspected coronary artery disease, no MI, baseline serum creatinine below 110 umol/L, no LV dysfunction with LVEF <45%,no blood electrolyte disturbances or liver dysfunction, 18-80 years age.	
Kooiman, 2014[33]	2	RCT/ Controlled	Yes	2009-2013	Inpatient (including ICU), Outpatient	Multi-center	Patients who were ≥18 years of age; CKD (eGFR < 60 mL/min/1.73m^2); Undergoing acute computed-tomography-pulmonary angiography; No pregnancy; No previous contrast administration within the past 7 days; No documented allergy for iodinated contrast media; No hemodynamic instability (systolic blood pressure < 100 mm Hg).	
Kotlyar, 2005[34]	2	RCT/ Controlled	No	NR	NR	Single-center	Elective coronary angiography and/or coronary intervention; no acute coronary syndrome requiring emergent coronary angiography or primary coronary intervention, no cardiogenic shock, no iodinated contrast media administration within a month or N -acetylcysteine within 48 h before the study entry, no current dialysis or a serum creatinine concentration N 1.4 mg/dL for men, or N 1.2 mg/ dL for women, no thyroid diseases, or no allergy to the study medication. Normal renal function (serum creatinine <1.4 mg/dl in men and <1.2 mg/dl in women).	
Krasuski, 2003[35]	2	RCT/ Controlled	Yes	NR	Inpatient (including ICU) Outpatient	Single-center	Elective cardiac catheterization; moderate renal insufficiency-Serum creatinine from 1.6mg/dl to 3mg/dl, Not requiring emergent or urgent procedures, not admitted for planned catheter based intervention, no absolute contra indication to or absolute indication for iv hydration, not on ACE inhibitor within 72h of procedure, not received iodinated contrast, aminoglycoside or nephrotoxic agent within 96h of procedure.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Kumar, 2014[36]	2	RCT	Yes	NR	Inpatient (including ICU)	Single-center	All patients willing to undergo angiography and angioplasty with or without risk factors and patients who received maximum or less than maximum permissible dose of the dye calculated from 5x bodyweight (kg)/ serum creatinine in mg%. No patients who were and continuing on any nephrotoxic drugs, no patients already suffering from gout or serum uric acid levels >10mg/dl, no previous hypersensitivity or intolerance to allopurinol, no congestive heart failure or ejection fraction < 40% and ability to give consent.	
Yin, 2009[38]	2	RCT/ Controlled	No	2007 to 2008	Inpatient (including ICU)	Single-center	Coronary angiography and/or PCI,CVD; NYHA 1-3 (<4); CR <3	
Lawlor, 2007[37]	2	RCT/ Controlled	No	NR	Outpatient	Single-center	angiography for peripheral vascular disease and aneursymal disease; stable chronic renal impairment, Patients with serum creatinine concentrations greater than 140 mmol/L or estimated creatinine clearance < 50 mL/min were eligible, patients with stable, chronic renal insufficiency patients with hemodynamic stability, those who no medical reasons to not tolerate the hydration protocol, No known sensitivity to NAC (gastrointestinal intolerance, urticaria), and those able to provide informed consent.	
Lehnert, 1998[70]	1,2	RCT/ Controlled	No	NR	NR	Single-center	Angiography with at least 1.2 ml/kg/BW contrast medium dose (specific type of test was not listed as inclusion criterion); All patients with stable serum creatinine of at least 1.4mg/dl undergoing angiography with contrast medium dose of greater than or equal to 1.2ml/kg BW, non-pregnant women, no known allergy to contrast medium, no prior exposure to contrast medium in past 14 days before the start of the protocol, and no diagnosis of end-stage renal disease.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Li, 2011[39]	2	RCT/ Controlled	No	NR	Inpatient (including ICU)	Single-center	Elective coronary angiography, no changes in PCr ≥ 0.5 mg/dL in the 24 hours prior to the test, no advanced renal failure, or dialysis (stage 4 and 5 of the National Kidney Foundation classification 28), no pregnancy, no contrast allergy, no severe clinical heart disease, and/or ejection fraction (EF) <30%, no acute myocardial infarction in the previous 2 weeks or hemodynamic instability necessitating inotropic support, no uncontrolled hypertension, no liver disease, no chronic obstructive pulmonary disease, N-acetylcysteine or need for intercurrent serum therapy, and no significant concomitant disease, such as malignant tumors, uncontrolled diabetes mellitus, hypothyroidism, or hyperthyroidism.	
Li, 2014 [40]	2	RCT/ Controlled	No	NR	NR	NR	Undergoing PCI; No patients who used drugs with renal toxicity at the preoperative period; No severe hepatic and renal dysfunction (severe renal dysfunction was defined as an estimated glomerular filtration rate (eGFR)\30 ml/min/1.73 m2); No tumor patients; No New York Heart Association class IV congestive heart failure or a left ventricular ejection fraction (LVEF) of\35 %; No thyroid or adrenal dysfunction; No acute or chronic infectious diseases, or hyperpyrexia.	
Liu, 2013[41]	2	RCT/ Controlled	Yes	2011 to 2012	Inpatient (including ICU)	Single-center	18-75 years of age; undergoing coronary angiography or PCI; mild to moderate kidney disease; No acute renal failure, unstable renal function or ESRD requiring dialysis; no hemodialysis. No uncontrolled diabetes mellitus, hypertension, or hyperthyroidism; NYHA class III or below heart failure or LVEF >35%; no IV or IA CM within seven days of the study or 3 days after; no NAC administration; no nephrotoxic agents 24 hours before or after procedure; no ascorbic acid within 30 days prior to the procedure.	
Ludwig, 2011[42]	1,2	RCT/ Controlled	No	2002 to 2004	NR	Single-center	Cardiac catheterization- angio-CT; 1.7mg/dl, NO patients already undergoing dialysis, no patients who had acute renal failure, or patients who had received iodinated contrast media within 7 days prior to the study. no patients with a known allergy to MESNA, no pregnant women, and no patients receiving dopamine, mannitol, or NAC.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Maioli, 2008[43]	2	RCT/ Controlled trial	No	2005 to 2006	Inpatient (including ICU)NR	Single-center	Coronary angiography; Chronic Kidney Dysfunction; No creatinine clearance ≥ 60 ml/min, no administration of contrast medium within the previous 10 days, no end stage renal disease	
Maioli, 2011[44]	2	RCT/ Controlled	Yes	2004 to 2008	NR	Single-center	Candidate for primary PCI with STEMI, No end stage renal failure requiring dialysis, No contrast media given within the previous 10 days.	
Manari, 2014[45]	2	RCT/ Controlled	No	2007 to 2010	Inpatient (including ICU)	Multi-center	>18 years of age; undergoing PCI; has a STEMI; chest pain for at least 30 min with ST=segment elevation of 0.2mV or more in at least 2 contiguous leads or new left bundle branch block; no mechanical complications; no previous peritoneal or hemodialysis treatment; no postanoxic coma; not pregnant.	
Marenzi, 2012[47]	2	RCT/ Controlled	No	2008 to 2011	Inpatient (including ICU)	Single-center	>18years and <85yearsv, coronary angiography and, when indicated, percutaneous coronary intervention (PCI), CKD- eGFR < 60 ml/min/1.73 m^2 no primary or rescue PCI and angiography procedures requiring a direct renal injection of contrast, no cardiogenic shock, no overt congestive heart failure, no acute respiratory insufficiency, no recent acute kidney injury, no chronic peritoneal or hemodialysis treatment, no known furosemide hypersensitivity, no receipt of intravenous contrast within 10 days before the procedure or another planned contrast-enhanced procedure in the following 72 h, and no contraindications to placement of a Foley catheter in the bladder.	
Marron, 2007[48]	2	RCT/ Controlled	No	NR	Emergency department	Single-center	Emergency contrast-enhanced CT; Renal insufficiency-serum creatinine concentration greater than 106 μmol/L (1.2 mg/dL), no pregnancy, no end-stage renal failure necessitating dialysis, no suspicion of acute renal obstruction (complicated renal colic), no asthma, no severe cardiac failure or hemodynamically unstable condition contraindicating IV hydration, and no non-urgent indications for CT.	
Ng, 2006[50]	2	RCT/ Controlled	Yes	NR	Inpatient (including ICU) Outpatient	Single-center	Cardiac catheterization, Cr>1.2,	
Oguzhan, 2013[51]	2	RCT/ Controlled trial	No	2010 to 2011	Inpatient (including ICU)	Single-center	Serum creatinine concentration of < 2.1 mg/dL. No acute STEMI, manifest congestive heart failure, hemodynamic instability, prior exposure to contrast media within 7 days, or use of a nephrotoxic drug within 48 h and contraindication for amlodipine and valsartan prescription	
Ozhan, 2010[52]	2	RCT/ Controlled	No	NR	NR	Single-center	Coronary or peripheral angiography and or PCI; CR > 1.5, creatinine clearance <60ml/min	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Pakfetrat, 2009[53]	2	RCT/ Controlled trial	No	2007 to 2008	Inpatient (including ICU)	Single-center	Coronary angiography or percutaneous coronary intervention; No recent (two days) exposure to contrast media, hypotension, intra-aortic balloon pump, pulmonary edema, dialysis, electrolyte and acid base disturbances, known sensitivity to AZ, not receiving therapies affecting renal function, for example mannitol, dopamine, and theophylline, or unwilling to give written informed consent	
Ratcliffe, 2009[54]	2	RCT/ Controlled	No	2007 to 2008	Inpatient (including ICU) Outpatient	Single-center	Coronary angiography or coronary angioplasty; elevated serum creatinine (greater than 132.6 µmol/L in men, and greater than 114.9 µmol/L in women) or reduced calculated creatinine clearance (less than 1.002 mL/s) using the Cockcroft-Gault formula, DM on oral antiglycemic or insulin therapy, no acute MI, no Signs of heart failure or EF <35%, no cardiogenic shock, no hypertrophic or restriction cardiomyopathy, no contrast media exposure in last week, no previous reaction to contrast media, no renal transplantation, no dialysis, no severe comorbid illness, no use of dopamine, mannitol, or fenoldopam, no newly diagnosed uncontrolled DM, no inability to follow-up	
Recio-Mayoral, 2007[55]	2	RCT/ Controlled	No	2004 to 2005	Inpatient (including ICU)	Single-center	PCI; Other Risk factors, MI, Patients with MI treated with primary PCI or rescue PCI, as well as patients with high-risk non–ST-segment elevation ACS needing urgent revascularization, were included. NO patient with end-stage renal failure on dialysis, uncontrolled hypertension (systolic blood pressure 160 mm Hg and/or diastolic blood pressure 100 mm Hg) and signs of cardiac failure not responding to medical treatment, No known severe aortic valve stenosis (area 1.0 cm2), No allergy to iodated contrast or NAC, and not pregnancy	
Reinecke, 2007[56]	2	RCT/ Controlled	No	2001 to 2004	Inpatient (including ICU)	Single-center	Elective coronary angigraphy; Serum creatinine concentrations ≥1.3 mg/dl and ≤3.5 mg/dl. Absence of acute or recent (within 30 days) myocardial infarction, congestive heart failure (New York Heart Association class IV), recipient of transplanted organs, monoclonal gammopathy, and/or previous contrast medium administration within 7 days	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Rosenstock, 2008[57]	2	RCT/ Controlled	No	NR	NR	Single-center	Coronary angiography, chronic kidney disease (CKD) stages 3–4 (glomerular filtration rate 15–60 ml/min/1.73 m^2, no acute ST elevation myocardial infarction within 2 weeks, no New York Heart Association functional class IV heart failure, no acute renal failure preceding angiography (defined as an increase in serum creatinine of [0.5 mg/dl from baseline values), no hyperkalemia (K[5.0 meq/l), GFR B15 ml/min/1.73 m^2 as calculated by the abbreviated MDRD formula, no prior cardiac catheterization within one month, no hemodynamic instability (defined as SBP\90 on at least two consecutive readings or patients requiring pressors), no poorly controlled hypertension (systolic blood pressure [180 mmHg on at least two consecutive readings), no patients taking combination ACEI/ARB therapy. no patients that had taken the ACEI or ARB less than 24 h before enrollment and randomization	
Schmidt, 2007[58]	2	Des_Pro	No	2002 to 2005	Inpatient (including ICU)	Single-center	Coronary angiography; to have received at least one 600mg oral dose of NAC before the procedure, no carotid or vascular angiographies performed instead of coronary angiography, no NAC administered before angiography	
Shehata, 2014[59]	2	RCT/ Controlled	Yes	201 to 2013	NR	NR	Diabetic with mild to moderate CKD (eGFR 30-90 ml/min/1.73 m^2); No severe CKD (eGFR <30 ml/min/1.73 m2); No end-stage renal disease (or patients on hemodialysis); No acute myocardial infarction requiring emergency coronary intervention; No cardiogenic shock; No history of acute coronary syndrome; No history of PCI or coronary artery bypass graft surgery; No congenital heart disease or any myocardial disease apart from ischemia; No limited life expectancy due to coexistent disease, for example, malignancy; No positive preprocedural cTnI result; No previous treatment with trimetazidine; No contraindications for aspirin, clopidogrel, or trimetazidine use (Parkinson disease and other motion disorders).	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Shemirani, 2012[71]	2	RCT/ Controlled	No	2006 to 2007	Inpatient (including ICU)	Single-center	Percutaneous coronary intervention; included patients with serum Cr < 1.5 mg/dL or glomerular filtration rate > 60 mL/min, no consumption of both captopril and furosemide, no PCI during acute myocardial infarction, heart failure of class III–IV New York Heart Association (NYHA), no previous exposure to contrast media in the 14 days before randomization, no need for emergency coronary artery bypass graft (CABG) during PCI.	
Solomon, 1994[60]	2	RCT/ Controlled trial	No	NR	NR	Single-center	Cardiac angiography; Cr>1.8	
Stevens, 1999[61]	2	RCT/ Controlled trial	Yes	NR	NR	Single-center	Elective coronary angiography; baseline SrCr > 1.8 mg/dl; Other Risk factors, No acute myocardial infarction requiring primary or rescue coronary intervention, no use of vasopressors prior to the procedure, no cardiogenic shock, no current peritoneal or hemodialysis, no planned postcontrast dialysis, no allergies to the study medications; Exclusion criteria included acute myocardial infarction requiring primary or rescue coronary intervention, use of vasopressors prior to the procedure, cardiogenic shock, current peritoneal or hemodialysis, planned postcontrast dialysis, or allergies to the study medications	
Talati, 2012[62]	1,2	Des_Pro	No	NR	NR	Single-center	Underwent catheter based coronary procedure	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Tamura, 2009	2	RCT	No	NR	Inpatient	Multi-center	>20 years and serum creatinine (Cr) level 1.1 to 2.0 mg/dl, No allergy to contrast medium, no pregnancy, no history of dialysis, no exposure to contrast medium within the preceding 48 hours of the study, acute coronary syndrome within the preceding 1 month of the study, no severe symptoms of heart failure (New York Heart Association functional class IV),no left ventricular ejection fraction _25%, severe chronic respiratory disease, no single functioning kidney, and no administration of *N*-acetylcysteine, theophylline, dopamine, or mannitol.	
Trivedi, 2003[63]	2	RCT/ Controlled	No	NR	Inpatient (including ICU).	Single-center	Non-emergency coronary angiography calculated creatinine clearance greater than 20 ml/min, Absence of clinically decompensated heart failure and states of decreased effective arterial volume (such as nephrotic syndrome, cirrhosis of liver). Willingness of the participant to participate. Approval by the patient's primary treating team.	Some patients were known to be in the hospital at baseline; the paper does not specify if some patients were recruited from an outpatient setting as well

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Weisberg, 1994[64]	2	RCT/ Controlled	No	NR	NR	Single-center	Elective cardiac cath; Cr >= 1.8 mg/dL, Absence of the following: NYHA Class IV congestive heart failure, evidence of liver dysfunction, hemodynamic instability, allergy to contrast medium, prior exposure to contrast medium within seven days of the experimental protocol, pregnancy.	
Wolak, 2013[65]	2	RCT/ Controlled	No	2010 to 2010	NR	Single-center	>18 years of age; Chronic therapy of >1 month with ACE and/or ARB; Undergoing coronary angiography; No chronic use of non-steroidal anti-inflammatory and cyclo-oxygenase-2 selective inhibitors; No chronic treatment with mineralocorticosteroid receptor blocker; No chronic treatment with renin antagonist; Systolic blood pressure >90 mmHg; No administration of contrast within 14 days of enrollment.	
Xinwei, 2009[66]	2	RCT/ Controlled trial	No	2007 to 2008	Inpatient (including ICU)	Single-center	Percutaneous Coronary Intervention; Other Risk factors, Acute Coronary Syndrome: ACS was defined as any one of the following: (1) unstable angina pectoris; (2) ST-segment elevation myocardial infarction; and (3) non–ST-segment elevation myocardial infarction; ; The following exclusion criteria were used: pregnancy, lactation, previous contrast media exposure within 7 days of study entry, acute renal failure, end-stage renal disease requiring dialysis, alanine transaminase elevation, history of hypersensitivity to contrast media, multiple myeloma, cardiogenic shock, and left ventricular ejection fraction 40%. Also, patients who had used statins within 30 days were excluded. Patients who had undergone primary PCI or had undergone PCI within 5 days after enrollment were excluded from the present study	
Yavari, 2014[67]	2	RCT/ Controlled trial	No	2011 to 2012	Inpatient (including ICU)	Single-center	18-65 years of age; undergoing PCI; baseline SCr ≤132.6 lmol/l (1.5 mg/dl); No acute myocardial infarction, congestive heart failure, hemodynamic instability during or after the procedure, known allergy or previous administration of pentoxifylline, and use of concomitant nephrotoxic agents (e.g. non-steroidal anti-inflammatory drugs, aminoglycosides, recent contrast injection, etc.) or diuretics.	

Evidence Table I-2. Study characteristics for studies comparing interventions to prevent development of CIN (continued)

Author, Year	Key Question	Design	Sub group analysis	Recruitment date	Recruitment setting	Multi or single center	Inclusion criteria	Comments
Yin, 2013[68]	2	RCT/ Controlled	No	2009 to 2010	Inpatient (including ICU)	Single-center	Primary or urgent coronary angioplasty; Other Risk factors, patients with acute ST elevation myocardial infarction (STEMI) requiring primary coronary intervention and acute non-ST elevation myocardial infarction (NSTEMI) requiring urgent coronary intervention, Patients presenting within 12hrs after onset of symptoms. No patients with cardiogenic shock Patients with Scr <3.0 mg/dl and patients not on long-term dialysis	

ACE= Angiotensin Converting Enzyme, ACEI=Angiotensin Converting Enzyme Inhibitor, ACS=Acute Coronary Syndrome, AMI=Acute Myocardial Infarction, ARB=Angiotensin Receptor Blocker, ARF=Acute Renal Failure, AZ=Acetazolamide, BW=Body Weight, CABG=Coronary Artery Bypass Grafting, CAG= Coronary angiogram, Cc/kg=cubic centimeter per kilogram, CE-MDCT=Contrast Enhanced Multi-detector Computer Tomography, CHF=Chronic Heart Failure, CIN=Contrast Induced Nephropathy, CKD=Chronic Kidney Disease, CM=Contrast Media, Cr=Creatinine, CrCl=Creatinine Clearance, CRF=Chronic Renal Failure, CT=Computer Tomography, CVD=Cardiovascular Disease, EF=Ejection Fraction, eGFR=estimated Glomerular Filtration Rate, ESRD=Endstage Renal Disease, GFR=Glomerular Filtration Rate, GI=Gastrointestinal, H=hour, HD=Hemodialysis, IA=Intrarterial, ICU=Intensive Care Unit, IV=Intravenous, LDL=Low Density Lipoprotein, LVEF=Left Ventricular Ejection Fraction, MDCT=Multi-detector Computer Tomography, MDRD= Modification of Diet in Renal Diseases, mEq/l=milliequivalents per liter, Mg/dl=milligrams per deciliter, mg=milligram, MI=Myocardial Infarction, Ml/min/1.73m^2=milliter per minute per 1.73 meter squared, Ml/min=milliliter per minute, mmHG=millimeter of Mercury, Mol/l=mole per liter, NAC=N-acetylcysteine, NR=Not Reported, NSAID=Non-steroid Inflammatory Drug, NYHA=New York Heart Association, PCI=Percutaneous Coronary Intervention, PCr=Plasma Creatinine, RCT=Randomized Controlled Trial, SrCr=Serum Creatinine, STEMI= ST Elevation Myocardial Infarction, T2DM=Type 2 Diabetes Mellitus, Umol/l=micromole/liter, Yrs=years

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN.

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Abizaid,1999[1]	Low osmolarity contrast medium (Hexabrix, Mallinkrodt, St. Louis, Missouri)	IA	Not specified, Define, mean 202 ml. Range75-450ml	1	0.45% IV Normal Saline (1 ml/kg/hour)	IV	1 ml/kg/h 0.45% IV normal saline, Saline 12hrs before and 12hrs after, Prior to CM administration After CM admin	All patients received 0.45% normal saline (1 ml/kg/h)
				2	Dopamine (2.5 ug/kg/min) plus 0.45% IV Normal Saline (1 ml/kg/hour)	IV	2.5 ug/kg/min dopamine + 0.45% IV normal saline hydration 1ml/kg/h, Saline 12hrs before and 12hrs after-others not stated, Prior to CM administration After CM admin	
				3	Aminophylline (4 mg/kg followed by a drip of 0.4 mg/kg/hour) plus 0.45% IV Normal Saline (1 ml/kg/hour)	IV	4 mg/kg aminophylline followed by a drip of 0.4 mg/kg/hr+0.45% IV normal saline hydration 1ml/kg/hour, Saline 12hrs before and 12hrs after-others not stated, Prior to CM administration After CM admin	
Acikel, 2010[2]	Iohexol	IA	66-260ml. Comparable between groups	1	Control	NR		Saline 1ml/kg/h 4h prior until 24 after procedure
				2	Atorvastatin	Oral	40mg/d, 3 days, Prior and after CM administration	Saline 1ml/kg/h 4h prior until 24 after procedure
				3	Chronic statins	Oral	At least a month, Prior and after CM administration	Saline 1ml/kg/h 4h prior until 24 after procedure
Adolph, 2008[3]	Iodixanol	IA	Mean Arm 1 138 +/- 52 ml Arm 2 141 +/- 50 ml	1	Saline plus dextrose	IV	154 mEq/l of sodium chloride in 5% dextrose solution , 2 ml/kg of body weight per hour for 2 hr before, at a rate of 1 ml/kg of body weight per hour during, and for 6 h after the administration of iodixanol.	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Adolph, 2008[3] (continued)				2	Sodium Bicarbonate in 5% dextrose	IV	154 mEq/l of sodium bicarbonate in 5% dextrose solution, 2 ml/kg of body weight per hour for 2 h before, at a rate of 1 ml/kg of body weight per hour during, and for 6 h after the administration of iodixanol.	
Alessandri, 2013 [4]	Iomeprol	IA	1.5ml-3ml/kg, Not specified	1	Sodium Chloride infusion	IV	Saline 0.9% 500mls thrice daily, 12hrs before and a day after, Prior to CM administration During CM administration After CM administration	
Alessandri, 2013 [4] (continued)				2	Sodium bicarbonate + NAC	Oral, IV	NAC 600mg bid + 160 meq of Na 2 HCO 3 in 350 ml of 5% glucose solution 2 ml/kg/h, NAC-day before to day after, nahco3-2hrs before to 6hrs after, Prior to CM administration During CM administration After CM administration	
Allaqaband, 2002 [5]	LOCM	IA	Mean: Arm1 1.47 ml/kg (SD 0.80), Arm2 1.52ml./kg (SD 0.81), Arm3 1.63ml/kg (SD 0.67), Not specified	1	0.45% saline	IV	0.45% Saline: 1 ml/kg/h, 12 hour before procedure, during procedure, and 12 hours after procedure, Prior to CM administration During CM administration After CM administration	
				2	0.45% saline + nac	IV	Saline: 1 ml/kg/h + NAC: 600mg 2x daily, Saline same as Arm 1, NAC: given 12 hours before and 12 hours after procedure, Prior to CM administration During CM administration After CM administration	
				3	0.45% saline + fenoldopam	IV	Saline: 1 ml/kg/h + Fenoldopam: 0.1 microgram/kg/hr, Saline: same as Arm 1, Fenoldopam: starting 4 hours before procedure and ending 4 hours after., Prior to CM administration During CM administration After CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
				2	N-acetylcysteine	Oral	600mg b.i.d, 24hrs before and 24hrs after, Prior and After CM administration	
Aslanger, 2012 [6]	Ioxaglate	IA	Not specified, Define, Mean: Arm1 - 204ml, Arm2 - 193ml, Arm3 - 205ml	1	Placebo	IV	12ml saline during procedure, placebo capsules presumably twice daily for 2 days, 48 hours, During CM administration After CM administration	0.9% saline for 12 hours at 1 ml/kg/h
				2	IV NAC	IV	1200mg IV during procedure, 1200mg by mouth twice daily for 2 days, 48 hours, During CM administration After CM administration	
				3	IA NAC	Other, IA	600mg IA before procedure, 1200mg by mouth twice daily for 2 days, 48 hours, Prior to CM administration After CM administration	
				2	NAC	Oral	600mg, 72 hours, Prior to CM administration During CM administration After CM administration	2 doses prior to procedure, 2 doses day of procedure, 1 dose after procedure
Bader,2004 [7]	Iohexol, Iopromide, LOCM	IA	Arm 1:mean 217ml Arm 2 mean 205ml Dose/duration not specified	1	Saline infusion before and after procedure	IV	2000ml/24hours, 12h before and 12h after, Prior to CM administration After CM administration. All patients allowed oral hydration after procedure.	Total volume of saline=2000mls. Type of saline not specified.
				2	Saline infusion during procedure	IV	300ml bolus, Bolus during procedure, During CM administration. All patients allowed oral hydration after procedure.	300mls bolus. Type of saline not specified.

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Baskurt, 2009[8]	LOCM, Other description, Ioversol	IA	Not specified	1	Hydration	IV	1 ml/kg/h for 12 h before and after contrast exposure, 12 h before and after contrast exposure, Prior to CM administration After CM administration	
				2	Hydration + N-acetylcysteine	Oral, IV	1 ml/kg/h of Isotonic Saline for 12 h before and after contrast exposure + NAC: 600 mg p.o. Twice daily the preceding day and the day of angiography, 12 h before and after contrast exposure, Prior to CM administration	
				3	Hydration + N-acetylcysteine + theophylline	Oral, IV	1 ml/kg/h of isotonic saline for 12 h before and after contrast exposure. NAC + theophylline (600 mg NAC p.o. And 200 mg theophylline p.o. Twice daily for the preceding day and the day of angiography, 12 h before and after contrast exposure, Prior to CM administration	
Brar, 2014[9]	Ioxilan	IA	Dose: 350 mg iodine/ml Volume: NR Duration: NR	1	IV Normal Saline	IV	0.9% Saline infusion 3ml/kg for 1 hr before CM +1.5 ml/kg/h, 5 hr (1h pre - 4h post)	
				2	LVEDP-guided IV hydration	IV	0.9% Saline infusion 3ml/kg for 1 h before CM +5ml/kg/h LVEDP <13mmHg - 3ml/kg/h LVEDP =13-18 mmHg 1.5 ml/kg/h LVEDP >18mmHg, 5 h (1h pre - 4h post)	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Briguori, 2004 [10]	Iodixanol,	IA	Not specified, Define, Mean: Arm1 160 (SD 82), Arm2 168ml (SD 104)	1	0	NR		
				2	NAC + saline	Oral, IV	0.45% saline 1ml/kg, 1,200mg NAC twice daily = 4800mg total, 48 hours, Prior to CM administration During CM administration After CM administration	Saline given before and after procedure, NAC given day before and day of procedure
				3	Fenoldopam mesylate + saline	Oral, IV	0.45% saline 1ml/kg, Fenoldopam given at 0.10 ug/kg/min, 24 hours, Prior to CM administration During CM administration After CM administration	Saline given before and after procedure, Fenoldopam started 1 hour before procedure and continued through till 12 hours after.
Briguori, 2004[11]	Other description, Iobitriolol	IA	Not specified, Mean: Arm2 184ml (SD 122), Arm3 174 ml (SD 108)	1	0			All pts had saline 0.45% 1/ml/kg 12h before-12h after CM
				2	NAC single dose	Oral	NAC 600g bid, 2 days, Prior to CM administration After CM administration	1 day before-1 day after CM
				3	NAC double dose	Oral	NAC 1200 mg bid, 2 days, Prior to CM administration After CM administration	1 day before-1 day after CM
Briguori, 2007[12]	Iodixanol	IA	Dose and duration not specified. Mean volume: Arm 1: 179ml, Arm 2: 169ml, Arm 3: 169ml	1	IV Normal Saline + oral NAC	Oral, IV	IV 0.9% saline, 1ml/kg/h, 12 hours before and 12 hours after contrast media administration. NAC given at 1200mg twice daily the day before and day after procedure.	All patients given Arm 1 intervention.
				2	IV NaHCO3 + oral NAC	Oral, IV	154mEq/L sodium bicarbonate in dextrose and water. Initial bolus 3ml/kg/h given 1 hour before contrast media, 1ml/kg/h during procedure and for 6 hours after.	All patients given Arm 1 intervention, along with sodium bicarbonate.
				3	IV Normal Saline + IV ascorbic acid + oral NAC	Oral, IV	3g of ascorbic acid IV 2 hours before contrast media, and received 2g the night and morning after procedure.	All patients given Arm 1 intervention, along with ascorbic acid.

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Briguori, 2011 [13]	Iodixanol	IA	Not specified	1	IV Sodium bicarbonate + oral NAC	Oral, IV	IV 154 meq/L sodium bicarbonate, 1200mg NAC twice daily for 2 days, 7 hours sodium bicarbonate, 2 days NAC, Prior to CM administration During CM administration After CM administration	
				2	RenalGuard: IV 0.9% saline + IV NAC + RenalGuard System + IV furosemide	Oral, IV	Furosemide 0.25 mg/kg, NAC 1500mg, ~ 8 hours, Prior to CM administration During CM administration After CM administration	Includes hydration with 0.9% saline and use of renalguard system. Renalguard system includes a closed-loop fluid management system, a high-volume fluid pump, a high-accuracy dual weight measuring system, motion-detection artifact reduction, a single-use intravenous set and urine collection system that interfaces with a standard Foley catheter, real-time display of urine and replacement fluid volume, timely alerts to drain the urine bag or to replace the hydration fluid bag, and safety features such as automatic air and occlusion detection.
Chen, 2008[14]	IOCM	IA	mean 285 +/- 107 (for both groups with normal renal function), 298 +/- 125 (for both groups with abnormal renal function), Not specified	1	Normal renal function-Non hydration	Other, usual care	NR	Non-hydration intervention not specified
				2	Normal renal function-0.45% saline	IV	Saline 0.45% 1ml/kg/h, 18h, Prior to CM administration After CM administration	
				3	Abnormal renal function-NAC + Non hydration	Oral	NAC 1200 mg bid, 18h, Prior to CM administration After CM administration	Non-hydration intervention not specified
				4	Abnormal renal function-NAC+-0.45% saline	Oral, IV	NAC 1200 mg bid + Saline 0.45% 1ml/kg/h, 18h, Prior to CM administration After CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Cho, 2010 [15]	Isoversol	IA	320mg iodine/ml, duration not specified, 118-136 ml	1	IV 0.9% saline	IV	Saline infusion 3 ml/kg/h 1 h pre - 1ml/kg/h 6 h after, 7H, Prior to CM administration During CM administration After CM administration	154 meq, normal saline
				2	IV sodium bicarb + IV 0.9% saline	IV	Sodium bicarb infusion 3ml/kg/h 1 h pre - 1ml/kg/h 6 h after, 7H, Prior to CM administration During CM administration After CM administration	154 meq
				3	Oral fluids (water)	Oral	Water 500 ml 4 hr before procedure stop 2 hr prior + 600 ml after procedure, 2 hr, Prior to CM administration After CM administration	
				4	Oral fluids (water) + oral bicarb	Oral	Water 500 ml 4 h before procedure-stop 2 hr prior + 3.9g sodium bicarb oral 20 min before procedure +600 ml after procedure, 2H, Prior to CM administration After CM administration	46.4 meq
Demir, 2008 [16]	Iomeprol, Iopamidol	IV	100ml: Iomeprol (61.25 g/ml) Iopamidol (61.25 g/ml), Not specified, Define, 100ml: Iomeprol (61.25 g/ml) Iopamidol (61.25 g/ml)	1	Saline	IV	2000ml 0.9% saline hydration, 48 hours (24 pre and 24 post), and after CM administration	Normal saline given to all arms
				2	Saline +NAC (NAC)	Oral	Hydration as arm 1 + NAC 600 ml/d, 3 days prior, day of, 1 day post procedure	In the morning plus control
				3	Saline + Misoprostol (M)	Oral	Hydration as arm 1 + misoprostol 400 mg/d (200mg, 2x/day), 3 days prior, day of, 1 day post CM	Plus control
Demir, 2008 [16]				4	Saline + Theophylline (T)	Oral	Hydration as arm 1 + theophylline 200mg/d, 3 days prior, day of, 1 day post CM	In the morning plus control
				5	Saline + Nifedipine (N)	oral	Hydration as arm 1 + nifedipine 30 mg/day, 3 days prior, day of, 1 day post CM	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Durham, 2002[69]	Iohexol	IA	Mean: Arm1 48.1 min (SD 30.9), Arm2 44.8 min (SD 19.1), Define, Mean: Arm1 84.7 ml, Arm2 77.4 ml	1	IV hydration plus placebo	Oral	Saline 0.45% 1 ml/kg/h, placebo NR, 1h before and 3h after, Prior to CM administration After CM administration	Saline hydration given for 12 hours before and up to 12 hours after procedure All patients were placed on conventional iv hydration but actual rate and duration was left to physician
				2	IV hydration plus NAC	Oral	Saline 0.45% 1 ml/kg/h, 1200mg NAC, 1h before and 3h after, Prior to CM administration After CM administration	Saline hydration given for 12 hours before and up to 12 hours after procedure
Erol, 2013 [17]	Iohexol	IA	780mosm/kg +50mg iodine/mL, Not specified	1	Saline hydration	IV	1 mg/kg/h normal saline, 24 hours, Prior to CM administration After CM administration	12 hours pre and 12 hours post contrast
				2	Saline hydration + alloprinol	Oral, IV	300mg allopurinol + 1 mg/kg/hr normal saline, 24 hours, Prior to CM administration After CM administration	Allopurinol 24 hours before+ hydration: 12 hours pre and 12 hours post contrast
Firouzi, 2012[18]	Iodixanol, Iopromide	IA	325.34(101.41) vs 319.28(98.1) p=0.6	1	Control	NR	Normal Saline	
				2	Pentoxifylline	IV	Hydration as arm 1 + pentoxifylline 400mg 3xd for 2 days	
Frank, 2003[19]	Iomeprol	IA	mean dose was 80 mL; 3 CM injections into LCA and 2 injections into the RCA + biplane levocardiography using 25 mL	1	0.9% saline volume expansion	IV	1000 ml 0.9% saline, 12 Hours. Prior and After CM administration	6 hours pre and 6 hours post CM admin
				2	0.9% saline volume expansion + high-flux HD	control + HD	1000 ml 0.9% saline (same as control) + HD, saline duration was the same as in the control group; HD was over 4 hours during CM admin. Prior and After CM administration	Plus control regimen

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Gu, 2013 [20]	Not specified	IA	Not specified	1	Control--saline	IV	1ml/kg/h saline, From 4 h before to 24 hours after surgery, Prior to CM administration During CM administration After CM administration	New York Heart Association stage 2 and 3 had limited oral intake of fluids
				2	Furosemide	IV	20mg furosemide, over 30 seconds 7-13 minutes (~10.1 +/- 3.2 min) after procedure, After CM administration	This group also received same saline protocol as control
Gulel, 2005 [72]	Ioxaglate	IA	Not specified, Not specified	1	Control	NR		All patients received saline 1ml/kg/h infusion 12 h before-12 h after CM
				2	NAC	Oral	600mg bid, 2days, Prior to CM administration After CM administration	The day before and the day of the day of CM
Gunebakmaz, 2012[21]	Iopromide, LOCm	IA	61-64, Not specified, Not specified	1	Saline	IV	1ml/kg/h, 18 hours, staring 12 hours before the procedure, Prior, during and after CM administration	0.9% saline for all arms
				2	Saline + nebivolol	NR	600mg bid, 4 days, starting 2 days before the procedure, Prior, during and after CM administration	
				3	Saline + NAC	IV	5mg day, 4 days, starting 2 days before the procedure, Prior, during and after CM administration	
Hafiz, 2012 [22]	LOCM	IA	Not specified, Not specified	2	NS with or without NAC	Oral, IV	0.9% saline 1ml/kg, 1200mg NAC administered twice, 2400mg total, 24 hours saline, Prior to CM administration After CM administration	NAC administered 2-12 hours before procedure and 6-12 hours after procedure
				3	Sodium Bicarbonate with or without NAC	Oral, IV	154 meq/l NAHCO3 3ml/kg/hour, 1200mg NAC administered twice, 2400mg total, 7 hours NAHCO3, Prior to CM administration After CM administration	NAC administered 2-12 hours before procedure and 6-12 hours after procedure

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Hans,1998[23]	Iohexol, Other description, the brand is Omnipaque 300 (concentration is listed below under dose)	IA	OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL (per package insert), Not specified, Define, 140 ml (SD=29.6) for control group and 146 mls (SD=46) for dopamine group	1	Placebo	IV	NR, Does not specifically say, but may also be 12 hours (see below), Not stated	Article says that patients in the control group received an equal volume of normal saline. The timing is not stated. It may be the same timing as the dopamine, but it does not explicitly say Patients were encouraged to drink liquids before and after the arteriography (assumption is that this means all patients).
				2	Dopamine	IV	2.5 mcg/kg/min of dopamine, 12 hours, Prior to CM administration During CM administration After CM administration	It seems that the dopamine is continued during the contrast administration also (does not say it was stopped during that time, so it sounds like it is given prior, during, and after CM administration)
Hashemi, 2005 [24]	Other description, Meglumin compound	IA	370 mg/ 20ml, Define, 2 hours prior procedure to 48 hours after, Define, Mean: Arm1 223.3ml (SD 130), Arm2 225ml (SD 120)	1	Placebo	Oral	Placebo NR, 2 hours prior to procedure until 48 hours after procedure	All the patients had received aspirin 100 mg/d and ticlopidin 250 mg/bid from one week prior to angioplasty, and normal saline 0.9% infusion (total volume of 1.5 liter) at a rate of 60 ml/h from 12 hours before angioplasty until 12 hours after the procedure.
				2	Captopril	Oral	12.5mg captopril every 8 years, 2 hours prior to procedure until 48 hours after procedure, Prior to CM administration During CM administration After CM administration	
Heguilen, 2013 [25]	Ioversal	NR	Dose: 678mg/dose, duration not specified. Mean Volume: Arm2 179.8ml, Arm3 209.9 ml, Arm4 186.6ml	1	Sodium bicarbonate	IV	154 mmol nahco3, at 3ml/kg, 15 hours, Prior to CM administration During CM administration After CM administration	All arms fluid mixed with 5% dextrose

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Heguilen, 2013 [25] (continued)				2	NAC+NaHCO3	Oral, IV	600mg NAC, twice daily., 2 days, Prior to CM administration During CM administration	
				3	NAC + NaCl	Oral, IV	600mg NAC plus 154 mmol NaCl solution at 3 ml/kg/h, 2 days, Prior to CM administration During CM administration After CM administration	Saline solution given 2 hours before procedure and 12 hours after. NAC given in same schedule as Arm3
Holscher, 2008[26]	Iopromide	NR	Not specified	1	Hydration only	IV	500 ml 5% glucose and 500 ml 0.9% sodium chloride, 12 h before and after, Prior to CM administration After CM administration	
				2	Hydration plus dialysis	IV	500 ml 5% glucose and 500 ml 0.9% sodium chloride, 12 h before and after, Prior to CM administration After CM administration	
				3	Hydration plus NAC	Oral, IV	500 ml 5% glucose and 500 ml 0.9% sodium chloride plus 600mg NAC, NR, Prior to CM administration After CM administration	
Huber, 2006[27]	Iomeprol, Other description, Imeron	IA and IV	Not specified, Define, 100-400ml	1	0			
				2	Theophylline	IV	200 mg infusion 30 min before CM, short infusion, Prior to CM administration	Started 30min before contrast procedure. Hydration for all arms dependent on physician and patient condition.
				3	Acetylcysteine	IV	600 bid, 2 days, day before and day of procedure, Prior to CM administration During CM administration	Starting the day before. Hydration for all arms dependent on physician and patient condition.
				4	Theophylline + Acetylcysteine	IV	200 mg infusion 30 min before CM, 600mg bid of acetyl, 2 days, day before and day of procedure, Prior to CM administration	Starting the day before. Hydration for all arms dependent on physician and patient condition.

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kimmel, 2008[28]	Iomeprol	IA	Not specified	1	Placebo	Oral	NR, 48 h, Prior to CM administration During CM administration	Day before and day of procedure All patients received a peri-procedural intravenous infusion ('volume expansion') of 1 ml/kg/h with 0.45% saline for 24 h (12 h before and 12 h after exposure to CM)
				2	Nac	Oral	600mg b.i.d, 48 h, Prior to CM administration During CM administration	Day before and day of procedure
				3	Zinc	Oral	60mg daily, 24 hours, Prior to CM administration	Day before
Kinbara, 2010[29]	Iopamidol,	IA	0.755g/ml	1	Hydration	IV	1 ml/kg/h, 30min before and 10hs after angiography, prior and after CM administration	Arm 2: NAC and Arm 3: Aminophylline
				2	Hydration and aminophylline	IV	250mg +control treatment, 30min before + control treatment, Prior to CM administration	
				3	Hydration and N-acetylcysteine	Oral	704mg twice daily + control treatment, day before and during procedure + control, prior and during CM administration	
Klima, 2012 [30]	LOCM, IOCM	IA or IV	Not specified	1	0.9% saline	IV	0.9% saline, 1 ml/kg/h, ~20 hours, Prior to CM administration During CM administration After CM administration	Saline started at 8pm day before procedure and for at least 12 hours after procedure
				2	Long term sodium bicarbonate	IV	166 meq/L, ~8 h, Prior to CM administration During CM administration After CM administration	Sodium bicarbonate given for 1 hour before CM administration during CM administration and 6 hours after procedure
				3	Short term sodium bicarbonate	Oral, IV	166 meq/L + 500mg, 20 min, Prior to CM administration During CM administration	Given 20 min sodium bicarbonate though IV, and then 500mg sodium bicarbonate orally at start of infusion

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Koc, 2012[31]	Iohexol	IA	Dose and duration not specified. Volume Mean: Arm1 130ml, Arm2 130ml, Arm3 120ml	1	IV 0.9% saline	IV	0.9% saline 1 ml/kg/h, 12 h before and 12 h after the coronary procedure, Prior to CM administration After CM administration	
				2	IV NAC plus high-dose IV 0.9% saline	IV	IV bolus of 600 mg of NAC twice daily, before and on the day of the coronary procedure, Prior to CM administration During CM administration After CM administration	IV 0.9% saline 1 ml/ kg/h before, on and after the day of the coronary procedure
				3	IV 0.9% saline	IV	IV 0.9% saline 1 ml/kg/, before, on and after the day of coronary procedure, Prior to CM administration During CM administration After CM administration	
Kong, 2012 [32]	Iopromide	IA	Not specified	1	IV 0.9% saline	IV	12 h before the procedure and continued for 24 h after procedure, Prior to CM administration During CM administration After CM administration	Normal saline, 1ml/kg/h Duration is difficult to describe and details are under dose
				2	Oral hydration before and after procedure	Oral	500 ml 2 h before procedure and 2000 ml within 24 h following procedure, Prior to CM administration After CM administration	Tap water
				3	Oral hydration after procedure	Oral	2000 ml within 24 h following procedure, After CM administration	Tap water

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kooiman, 2014[33]	Iopromide, Iobitridol, Iodixanol	IA	Mean Iodine dose: Arm1: 24.9g, meant Arm2: 24.7g Mean Contrast Volume: Arm1: 74.5ml, Arm2: 73.5ml	1	No hydration	NR	No hydration administered before or after procedure.	No other CIN preventive treatments were used, such as oral hydration or NAC.
				2	IV 1.4% NaHCO3	IV	250ml IV 1.4% NaHCO3 1 h before procedure. No hydration given after procedure	No other CIN preventive treatments were used, such as oral hydration or NAC.
Kotlyar, 2005[34]	Iopromide, Other description, Ultravist-370, 0.769 mg/ml, 370mg iodine/ml; Schering Berlin, Germany	IA	Not specified, Define, mean 87ml in Arm 1, mean 89 ml in Arm 2 and mean 86ml in Arm 3	1	IV hydration	IV	0.9% saline commenced at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure, NR, Prior to CM administration After CM administration	All patients, scheduled for angiography, received written instruction to drink 1 l of fluid the evening prior to the procedure
				2	NAC 300mg	Oral	IV NAC 300mg +IV Hydration0.9% saline (NaCl at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure), NR, Prior to CM administration After CM administration	NAC was prepared in 100 ml of 5% dextrose and administered over 20 min, 1–2 h before angiography and again 2–4 h after angiography
				3	NAC 600mg	Oral	IV NAC 600mg +IV hydration0.9% saline (NaCl at 200 ml/h 2 h before angiography and continued for a further 5 h after the procedure), NR, Prior to CM administration After CM administration	NAC was prepared in 100 ml of 5% dextrose and administered over 20 min, 1–2 h before angiography and again 2–4 h after angiography
Krasuski, 2003[35]	Not specified	IA	Arm 1 mean=1.7cc/kg; Arm 2 mean 1.6cc/kg Arm 1 mean=136cc; Arm 2 mean=131cc	1	Overnight hydration dextrose plus saline	IV	5% dextrose in half normal saline - 1cc/kg/h, 12h before. Prior to cm administration	Upon completion of the study, all patients were encouraged to take oral fluids and received 12 hours of iv 5% dextrose in half normal saline at 1cc/kg/h
				2	Bolus normal saline	IV	Bolus-250cc normal saline, 20mins. Prior to CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Kumar, 2014[36]	Iohexol Iodixanol	IA	Iohexol: 350 mg Iodixanol: 320 mg	1	IV NS	IV	1ml/kg/hr, 12 hours before and after administration of radio contrast agent	
				2	Oral NAC + IV NS	Oral, IV	600 mg bd, 12 hours before and after administration of radio contrast agent	
				3	Allpurinol + IV NS	Oral, IV	300 mg/day, 12 hours before and after administration of radio contrast agent	
Lawlor, 2007 [37]	Not specified	IA	100-200mg, Not specified, Define, Arm 1 mean=163ml; Arm 2 mean=158; Arm 3 mean=165ml	1	IV 0.9% saline	Oral, IV	IV 0.9 NaCl 1 ml/kg/h+ placebo(3 ml of 0.9% NaCl in 30 ml of ginger ale), 112 h of IV hydration before and after, Prior to CM administration After CM administration	Placebo given at same time as NAC was given to Arm 2 Unlimited oral hydration was encouraged in the post procedure period in all groups
				2	IV 0.9% saline + NAC	Oral, IV	600 mg NAC in 30 ml of ginger ale orally twice daily the day prior to and the day of angiography and 12 h of IV hydration (0.9 NaCl 1 ml/kg/h) both prior to and following the procedure, 48hours, Prior to CM administration	
				3	Oral hydration + NAC	Oral	NAC (600 mg in 30 ml of ginger ale orally twice daily the day prior to and the day of angiography)+outpatient oral hydration preparation of 1,000 ml water in the 12 h prior to the procedure + followed by IV hydration (0.9 NaCl 1 ml/kg/h) beginning 1-2 h prior to the procedure and continuing for a total of 6 h afterward, Prior to CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Lehnert, 1998 [70]	Iopentol, Other description, the concentration of the iopentol: 350 mg iodine/mL = 810 mOs/kg H2O)	IA and IV	3.0ml/kg(SD=0.4) for control and 3.5 ml/kg(SD=0.6) for the hemodialysis group, Not specified	1	Conservative treatment	IV	0.9% saline at 83 ml/hour, 24 hours (IVF beginning 12 hs before contrast, then continued at the same rate for 12 hours after contrast), Prior to CM administration After CM administration	All patients received 0.9% saline as described. If the patient was not on a calcium channel blocker, then 10 mg nitrendipine per 12 hours was scheduled beginning 12 hours before catheterization. Arm 1: IVF + oral Ca blocker if not on one (see above) Arm 2: IVF + HD + oral Ca blocker if not one (see above)
				2	Hemodialysis	Other, Vascular access shaldon catheter (femoral vein)	High flux polysulphone membrane, average blood flow 139 +/- 8 ml/min, dialysate flow 500 ml/min. No fluid withdrawal., 3 hours (also 24 hours of IVF as in the control group), After CM administration	All patients received 0.9% saline as described in Arm 1. If the patient was not on a calcium channel blocker, then 10 mg nitrendipine per 12 hours was scheduled beginning 12 hours before catheterization. Dialysis was started as soon as possible after termination of contrast (mean 63 +/- 6 min)
Li, 2011 [39]	Not specified	IA	Not specified	1	Control	NR	Normal Saline	Saline 1ml/kg/h infusion 6 h before- 6 h after All patients had 2 weeks washout for all ACEI before starting the trial
				2	Benazepril	Oral	Benazepril 10mg/day, 3 days, Prior to CM administration	Normal saline 1ml/kg/h infusion 6 h before- 6 h after
Li,2009 [38]	Iohexol	IA	Not specified, Define, 121 +/- 56 for arm 1, 116 +/- 65 for arm 2	1	Control	NR	Normal Saline	Saline 1ml/kg/h infusion for 12 h after CM
				2	Probucol	Oral	Probubcol 500mg bid, 3d before and after procedure	Saline 1ml/kg/h infusion for 12 h after CM

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Li, 2014 [40]	Iohexol	IA	Mean Volume: Arm1: 168 ml Arm2: 172 ml	1	IV Normal Saline	IV	0.9% saline IV for routine hydration only	Participants in hydration group were routinely offered antiplatelets, anticoagulation, antianginal agents, and conventional hydration treatment.
				2	IV Prostaglandin E1	IV	20 ng/kg/min IV prostaglandin E1, beginning1 hour prior to CM administration for 6 hours. Prior, during and after CM admin	
Liu, 2013[41]	Iodixanol	IA	Not specified	1	Statin	NR	40 mg/day, 12-24 hours prior and 7 days post procedure: Statins in all initially include patients. (Drug: N) 20mg atorvastatin: 59 40mg atorvastatin: 40 10mg rosuvatatin: 41 20mg simvastatin: 19 40mg fluvastatin: 11	If patients were on statin therapy prior to the procedure, their dose regimen was not changed (details on this were not provided beyond this statement). All patients received hydration (IV Normal saline, 1-1.5 ml/kg/h, 3-12 h pre and 6-24 hours post procedure).
				2	Statin plus alprostadil	IV	40 mg/day statin (see Arm1) + 20 mcg/day IV alprostadil, 1 day prior and 6 days post procedure	See notes for Arm 1. All patients received hydration (IV Normal saline, 1-1.5 ml/kg/h, 3-12 h pre and 6-24 hours post procedure).
Ludwig, 2011 [42]	Iomeprol	IA	Not specified, Define, 120-200 (comparable in both arms	1	Control	IV	Placebo before CM, NS, Prior to CM administration During CM administration After CM administration	Plus NaCl 1000 ml before and 500 ml after
				2	Mesna	IV	1600 mg MESNA before CM, NS (pulse regime), Prior to CM administration During CM administration After CM administration	Plus NaCl 1000 ml before and 500 ml after

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Maioli, 2008[43]	IOCM	IA	Not specified	1	IV Isotonic Saline plus oral NAC	IV, Oral	1ml/kg/h 0.9% Sodium Chloride plus oral NAC 600mg, twice day, 12h. Prior and After CM administration	The two arms also got oral NAC 600mg, twice daily, day before and day after the procedure in addition to the IV saline versus bicarbonate.
				2	IV Sodium Bicarbonate plus oral NAC	IV, Oral	1ml/kg/h 0.9% Sodium Chloride plus oral NAC 600mg, twice day, 1h, 6h. Prior and After CM administration	
Maioli, 2011 [44]	Iodixanol, IOCM	IA	Dose and duration not specified. Mean Volume: Arm1 224ml, Arm2 216 ml. Arm3 208ml	1	No hydration	No hydration	Not stated	
				2	Late IV 0.9% saline	IV	1ml/kg 0.9% saline solution, 12, After CM administration	
				3	Early IV sodium bicarbonate	IV	3ml/kg, 154 meq/L sodium bicarbonate, for 1 hour before and 12 hours after PCI, Prior to CM administration During CM administration After CM administration	
Manari, 2014[45]	Iodixanol	IA	Not specified	1	IV normal saline	IV	0.9% isotonic normal saline 1ml/kg/h, 12 hours.	All patients received 70-100 IU/kg unfractionated heparin; aspirin at 162 mg or more; 300/600 loading dose of clopidogrel
				2	High-dose infusion of IV normal saline	IV	0.9% isotonic normal saline 3ml/kg/h for 1 hour followed by normal saline 1 ml/kg/h for 11 hours	
				3	IV standard bicarbonate	IV	NaCOH3 solution: 154mEq/L sodium bicarb 1 ml/kg/h, 12 hours	
				4	High-dose IV bicarbonate	IV	NaCOH3 solution: 154mEq/L sodium bicarb 3 ml/kg/h for 1 h followed by 1 ml/kg/h for 11 hours	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Marenzi, 2006 [46]	Iohexol, LOCM, Other description, 350 mg of iodine per milliliter; Omnipaque, Amersham Health	NR	Define, Arm 1 mean 274;Arm 2mean= 264;Arm 3 mean= 253	1	Placebo	Other, NR		All treated patients and control patients underwent hydration with intravenous isotonic saline (0.9 percent) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram per hour in cases of overt heart failure) for 12 hours
				2	Standard dose NAC	Oral, IV	Total dose of 3000mg, Prior to CM administration After CM administration	Intravenous bolus of 600 mg of N-acetylcysteine before primary angioplasty and a 600-mg tablet orally twice daily for the 48 hours after intervention
				3	High dose NAC		Total dose of 6000mg, Prior to CM administration After CM administration	Intravenous bolus of 1200 mg of N-acetylcysteine before intervention and 1200 mg orally twice daily for the 48 hours after intervention
Marenzi, 2012 [47]	Iomeprol	IA	Not specified, Define, comparable between groups	1	Saline hydration	IV	Saline 0.9%1 ml/kg/h (0.5 ml/kg/h in case of left ventricular ejection fraction < 40%, 24 h infusion- 12h before and 12h after, Prior to CM administration After CM administration	Saline for all arms
				2	Furosemide plus matched hydration	IV	Furosemide- single IV bolus of 0.5 mg/kg (up to a max of 50 mg), over 30 min, Prior to CM administration Saline infusion 90mins before and up to 4h after	Saline infusion 90mins before and up to 4h after

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Marron, 2007[48]	Iodixanol	IA	Not specified	1	Isotonic 0.9% saline	IV	12h before and 12h after, Prior to CM administration After CM administration	Volume of iv fluid=2000mls in total
				2	Hypotonic 0.45% saline	IV	12h before and 12h after, Prior to CM administration After CM administration	
Mehran, 2009[73]	Iodixanol, Ioxaglate	IV	Not specified	1	0	IV	Diphenydramine 25 mg IV before and IV one-half isotonic saline at 100 ml/h for 3-5 h and for 12 h after CM administration During CM administration	N-acetylcysteine administered at discretion of investigator
				2	Iodixanol	IV	Diphenydramine 25 mg IV before and IV one-half isotonic saline at 100 ml/h for 3-5 h and for 12 h after CM administration During CM administration	N-acetylcysteine administered at discretion of investigator
				3	Ioxaglate			

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Mohamed,2008 [74]	Iohexol, LOCM	IA	Not specified, Define, Arm 1 mean(SD)=126.67(94.37)ml; Arm 2 mean (SD)=136.73 (100.23)ml	1	IV hydration	IV	Saline (0.45% NS) was given intravenously at a rate of I ml/kg/h 12 hours before and after coronary angiogram, 24h, Prior to CM administration After CM administration	
				2	IV hydration + oral NAC	Oral, IV	Oral NAC 600mg twice daily for four doses starting 12 hours before procedure + Saline (0.45% NS) was given intravenously at a rate of I ml/kg/h 12 hours before and after coronary angiogram, 24h, Prior to CM administration After CM administration	
Mueller,2002 [49]	LOCM, Other description, Ultravist 370; Schering, Berlin, Germany; and Imeron 350; Byk Gulden, Konstanz, Germany	IA	Dose and duration not specified. Mean Volume: Arm 1mean=232ml; Arm 2 mean=236ml	1	Isotonic Saline hydration	IV	1ml/kg of 0.9% saline, 24h, Prior to CM administration During CM administration After CM administration	Sodium concentration of 154mmol/l
				2	.45% sodium chloride plus 5% glucose	IV	1ml/kg of 0.45% sodium chloride plus 5% glucose, 24h, Prior to CM administration During CM administration After CM administration	Sodium concentration of 77mmol/l
Ng, 2006 [50]	Iodixanol, Iohexol, Ioxaglate	IA	Not specified, Define, 172.2 +/- 73.2 NAC group, 164.4 +/- 85.0 fenoldopam group	1	Hydration	IV	normal saline 1ml/kg/h, 1-2 h before CM and for 6-12 h after CM	All pts received hydration with normal saline
				2	NAC	Oral	NAC 600mg bid 4 doses, 2days, Prior and after CM administration	3 doses before CM - 1 dose after CM
				3	Fenoldopam	IV	0.1 mcg/kg/min, 8h, , during and after CM administration	Infusion started 2 h before CM

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Oguzhan, 2013[51]	Iopromide	IA	Not specified	1	AVH (amlodipine valsartan hydration group)	Oral, IV	5/160 mg; 1ml/kg/h, amlopidine/valsartan was given in 3 doses- one dose 24 h before the procedure, second on the morning before and third dose was given 24 h after contrast media exposure. Hydration therapy with isotonic NaCl was administered 12 h before and after contrast media exposure, both arm received hydration, prior and after cm administration	
Oguzhan, 2013[51] (continued)				2	H (hydration group)	IV	1ml/kg/h, Hydration therapy with isotonic NACL was administered 12 h before and after contrast media exposure, both arms received hydration, Prior and after CM administration	
Ozhan, 2010[52]	Iopamidol	IA	Not specified, Define, comparable between groups	2	Nac	Oral	NAC 600 mg twice daily, day after procedure, 1 day, After CM administration	Saline 1000 ml infusion for 6 h after procedure. Saline not specified.
				3	Nac + atorvastatin	Oral	NAC 600 mg and Atorvastatin 80 mg twice daily on day 1 after procedure. Atorv 80mg d for 2 days after procedure, 3 days, After CM administration	Saline 1000 ml infusion for 6 h after procedure. Saline not specified.
Pakfetrat, 2009[53]	IOCM (Iodixanol)	IA	Not specified	1	Sodium chloride	IV	1ml/kg/h normal saline in 5% dextrose, 6h before and 6h after. Prior and after cm administration	
				2	Sodium bicarbonate in dextrose solution	IV	3ml/kg/h before and 1ml/kg/h after, 1h before and 6hrs after. Prior and after cm administration	
				3	Sodium chloride plus oral Acetazolamide	IV	250mg, 2h before and 6h after. Prior and after cm administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Ratcliffe, 2009 [54]	Iodixanol, IOCM, Other description , nonionic 320 mg iodine/mL; 290 mOsm/kg water [Visipaque, GE Healthcare , USA	IA	Dose and duration not specified, Mean Volume; Arm 1mean=131, arm 2 mean=175, Arm 3 mean 169, arm 4 mean =125	1	IV normal saline	IV	NaCl (154 meq/L NaCl in 5% dextrose), at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure., 7 h, Prior to CM administration During CM administration After CM administration	All patients given saline or sodium bicarbonate in 5% dextrose.
				2	IV normal saline + IV/oral NAC	Oral, IV	IV bolus of 1200 mg of NAC 1 h before intervention and 1200 mg orally twice daily for 48 h after intervention + IV NaCl (154 meq/L NaCl in 5% dextrose), at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure, 2 days, Prior to CM administration During CM administration After CM administration	
				3	IV NaHCO3	IV	IV nahco3 (154 ml of 1000 meq/L nahco3 to 846 ml of 5% dextrose, slightly diluting the dextrose concentration to 4.23%) at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure., 7h, Prior to CM administration During CM administration After CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Ratcliffe, 2009 [54] (continued)				4	IV NaHCO3+ IV/oral NAC	Oral, IV	IV bolus of 1200 mg of NAC 1 h before intervention and 1200 mg orally twice daily for 48 h after intervention + nahco3 (154 ml of 1000 meq/L nahco3 to 846 ml of 5% dextrose, slightly diluting the dextrose concentration to 4.23%) at an infusion rate of 3 ml/kg/h for 1 h before contrast, and continued at 1 ml/kg/h during the procedure and for 6 h following contrast exposure, 2 days, Prior to CM administration During CM administration After CM administration	
Recio-Mayoral, 2007 [55]	Iomeprol, LOCM, Other description , Iomeron, Bracco s.p.a, Milan, Italy) with 350 mg/ml of iodine content	IA	Not specified, Define, Arm 1 mean+/-SD=279+/-94; Arm 2=290+/-114ml	1	Saline + NAC after procedure	Oral, IV	IV isotonic saline (0.9%) at rate of 1 ml/kg/h for 12 h after PCI + 2 doses of 600 mg NAC orally the next day, 24h, After CM administration	Standard institution protocol is perfusion with isotonic saline (0.9%) at rate of 1 ml/kg/h for 12 h after PCI
				2	IV Bolus+ NAC before procedure +NAC after procedure	IV	2400mg NAC in an IV bolus solution of 5 ml/kg/h of alkaline saline with 154 meq/l of sodium bicarbonate in 5% glucose and H2O (adding 77 ml of 1,000 meq/l sodium bicarbonate to 433 ml of 5% glucose in H2O) over 1 h, in the 60 mins before contrast + 1.5 ml/kg/h fluid therapy in the 12 h after the procedure + 2 doses of 600 mg NAC orally the next day, 24h, Prior to CM administration After CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Reinecke, 2007 [56]	Iopromide, IOCM, Other description, (Ultravist 370TM, Schering AG, Berlin, Germany).	NR	Arm1:mean 188; Arm 2 mean184; Arm3 mean197mg/dl, Not specified	1	Hydration only	IV	Glucose 5% + Saline 0.9% 24 h (1000 ml 12 h before- 1000ml 12 h after CM)	
Reinecke, 2007 [56] (continued)				2	Hydration + dialysis	IV, Other, hemodialysis	Glucose 5% + Saline 0.9% 24 h (1000 ml 12 h before- 1000ml 12 h after CM) Low-flux HD started within 20 min after procedure for 2 hours	
				3	Hydration + NAC	Oral, IV	Glucose 5% + Saline 0.9% 24 h (1000 ml 12 h before- 1000ml 12 h after CM) NAC 600 mg x4 (2 doses before and after)	One dose NAC 600 mg was given at the evening before catheterization, the second dose was given on the morning before catheterization; the third was given at the evening after catheterization and the last dose was given on the morning the day after angiography.
Rosenstock, 2008 [57]	IOCM, Not specified, Other description, 95% IOCM other 5% not specified	IA	Not specified, Define, Arm 1 125 +/- 75, arm 2 142 ± 76, arm 3 149 ± 90	1	Naive to angiotensin blockade	Other, No prior use of angiotensin blockade	N/a	79% had acetylcysteine + hydration(71%, 1/2 normal, 32% normal) Metformin and diuretics were withheld in all patients
				2	Continue angiotensin blockade during and after procedure	Other, Angiotensin blockade continued during and after procedure	N/a	74% had acetylcysteine (68%, 1/2 normal, 20% normal)

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Rosenstock, 2008 [57] (continued)				3	Discontinue angiotensine blockade morning of procedure and 24h after procedure	Other, angiotensin blockade stopped morning of procedure and 24h after procedure	N/a	78% had acetylcysteine + hydration(79%, 1/2 normal, 27% normal)
Seyon, 2007[75]	Iohexol	IA	147.5+/- 74.5 ml (tc); 133.68+/-58.04 (control)	1	Placebo + hydration	Oral	Placebo similar to NAC, once before procedure and then twice daily after for total of 4 doses. Prior and After CM administration	IV saline 0.45% 1 ml/kg/h; 4-6 hours pre and 12 hours post
				2	N-Acetylcysteine + hydration	Oral	600mg, once before procedure and then twice daily after for total of 4 doses. Prior and after cm administration	Iv saline 0.45% 1 ml/kg/h; 4-6 hours pre and 12 hours post
Shavit, 2009 [76]	Iopamidol	NR	755 mg iopamidol per milliliter, and 370 mg iodine per milliliter, Not specified	1	Sodium bicarbonate	IV	154 meq/L sodium bicarbonate in 5% dextrose. The initial IV bolus was 3 ml/kg for 1 hour before cardiac catheterization. Following this bolus, patients received the same fluid at a rate of 1 ml/kg per hour during the contrast exposure and for 6 hours after the procedure, Prior to CM administration During CM administration After CM administration	Bolus 3mefore procedure followed by infusion lml/kg/h for 12 hours Both arms 154 meq
				2	Sodium chloride + NAC	Oral, IV	NAC 600 mg× 2/d PO the day before and the day of the procedure., 2d, Prior to CM administration	12-hour infusion 1 ml/kg/h before cardiac catheterization

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Shehata, 2014[59]	Iopramide	IA	Dose: <4 ml/kg	2	IV Normal Saline + Oral NAC	Oral, IV	IV 0.9% normal saline (1 ml/kg/hour) starting 12 hours before PCI and up to 24 hours thereafter plus oral NAC (1,200 mg) was administered to patients in both groups, 24 hours before and after the procedure. Prior, during and after CM administration	Regimen given to all participants in study
				3	IV Normal Saline + Oral NAC + Oral Trimetazidine	Oral, IV	Oral trimetazidine (35 mg twice daily) for 72 hours, starting 48 hours before PCI. Prior, during and after Cm administration.	Also given IV 0.9% normal saline (1 ml/kg/hour) starting 12 hours before PCI and up to 24 hours thereafter plus oral NAC (1,200 mg) was administered to patients in both groups, 24 hours before and after the procedure. Prior, during and after CM administration
Shemirani, 2012 [71]	Other description, meglumine	IA	Not specified, Define, 120 ± 40 group a; 115 ± 57 group b; 133 ± 70 group c; 119 ± 42 group d	1	0			All patients received normal saline (0/9%) in a dose of 1 ml/kg/h 12 h before and 24 h after PCI
				2	Prior use of captopril then discontinued 36h before procedure	Oral	Not specified. About 36h before PCI, drug discontinued, 36h before PCI, drug discontinued, Prior to CM administration	
				3	Prior use of captopril continued during procedure	Oral	Not specified, Continued during procedure, Prior to CM administration During CM administration	
				4	Prior use of furosemide then discontinued 36h before procedure	Oral	Not specified. About 36h before PCI, drug discontinued, 3 h before PCI, drug discontinued, Prior to CM administration	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Shemirani, 2012 [71] (continued)				5	Prior use of furosemide continued during procedure	Oral	Not specified, Continued during procedure, Prior to CM administration During CM administration	
Solomon, 1994[60]	32% ionic high osm /32% ioinic low osm / 35% non ionic low osm	IA	Not specified	1	Saline	IV	1/ml/kg, 24h. Prior, during and after cm administration	Saline 0.45%
				2	Mannitol + saline	IV	25 mg, 60 min. Prior to cm administration	Saline 0.45%
				3	Furosemide + saline	IV	80 mg, 30 min. Prior to cm administration	Saline 0.45%
Stevens, 1999[61]	LOCM, HOCM (decision was made by operating physician)	IA	Not specified	1	IVF alone	IV	150ml/h of 0.45 NS before and during procedure then 6h after followed by hourly adjustment to match prior hour's urine output, before procedure, during procedure, and for at least 6 h after the procedure	Randomized to control or experimental arm, then the decision re: mannitol depended on the pulmonary capillary wedge pressure. All arms given 0.45 saline
				2	IVF + furosemide + dopamine + mannitol	IV	Furosemide 1mg/kg to max of 100mg single dose+ dopamine 3mcg/kg/min upon arrival to the catheterization lab and continued during the procedure + mannitol 12.5g in 250ml 5%dextrose (if PCWP < 20)+ control arm treatment, Before, during and at least 6 h after procedure	
				3	IVF + furosemide + dopamine	IV	Furosemide 1mg/kg to max of 100mg single dose+ dopamine 3mcg/kg/min upon arrival to the catheterization lab and during procedure (no mannitol if PCWP was at least 20)+ control arm treatment, Before, during and at least 6h after procedure	

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Talati, 2012 [62]	Iodixanol	NR	Not specified	1	No fenoldapam	NR	NR, NR, Not stated	All participants received hydration, not specified
				2	Fenoldopam	Other, intrarenal	Range: 0.1 - 0.4 ug/kg per min, Mean: 46.5 (SD: 5.5) min, Not stated,	
Tamura, 2009 [62]	Iohexol	IA	Not specified	1	Normal Saline	IV	Standard hydration with sodium chloride was intravenous administration with isotonic saline (0.9%) at a rate of 1 ml/kg/hour (0.5 ml/kg/hour for patients with left ventricular ejection fraction < 40%) for 12 hours before and 12 hours after an elective coronary procedure. For patients weighing >80 kg, infusion rate was limited to 80 ml/hour (40 ml/hour for patients with left ventricular ejection fraction < 40%).	
				2	Normal Saline + Bicarbonate	IV	Standard hydration with sodium chloride was intravenous administration with isotonic saline (0.9%) at a rate of 1 ml/kg/hour (0.5 ml/kg/hour for patients with left ventricular ejection fraction <40%) for 12 hours before and 12 hours after an elective coronary procedure. For patients weighing >80 kg, infusion rate was limited to 80 ml/hour (40 ml/hour for patients with left ventricular ejection fraction <40%).	
Thiele, 2010[77]	Iopromide	IA	Not specified, Define, median=180 ml	1	Placebo	IV	10ml of NaCl 0.9% before angio, 10 mls twice daily for 48h after PCI, 48 hours, Prior to CM administration After CM administration	After PCI, all treated and control patients underwent hydration with intravenous NaCl (0.9%) infusion at a rate of 1ml/kg of body weight per h for 12 h (or 0.5ml/kg/h in overt heart failure)
				2	NAC	IV	1,200mg twice daily, 6000mg, 48 hours, Prior to CM administration After CM administration	IV bolus of 1,200 mg before angioplasty and 1,200 mg intravenously twice daily for the 48 h after PCI (total dose 6,000 mg
Trivedi,2003 [63]	LOCM	IA	Dose and duration not specified. Mean Volume: Arm 1 mean=187.3 ml; Arm 2 mean=201.3	1	Oral hydration	Oral	Unrestricted fluids, Not stated	After catheterization, all subjects were routinely encouraged to partake oral fluids.

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Trivedi,2003 [63] (continued)				2	IV hydration(0.9% saline	IV	0.9% saline for 24 h at a rate of 1 ml/kg/h beginning 12 h prior to scheduled catheterization, 24h, Prior to CM administration During CM administration After CM administration	After catheterization, all subjects were routinely encouraged to partake oral fluids.
Weisberg, 1994 [64]	Other description, MD76 (66% diatrizoate meglumine, 10% diatrizoate sodium); it is an ionic, high-osmolality medium	IA	Not specified	1	Saline	IV	Saline 0.45% 100ml/h, 2h (not counting > 12 h of hydration pre-procedure; see below), During CM administration After CM administration Other, as below, all patients received IVF starting 1h pre-procedure	All patients received IV infusion of 0.45% NaCl at 100 cc/h beginning 12 hours before, and continuing throughout cardiac catheterization. Patients were randomly assigned to receive either saline or one of 3 drugs by IV infusion. The infusions began immediately after full instrumentation for cardiac catheterization and continued for a total of two hours (~ 2x the duration of the procedure).
				2	Dopamine	IV	Dopamine 2ug/kg/min in 0.45% NS at 100 ml/h, 2h, During CM administration After CM administration Other, as below, all patients received IVF starting 12 hours pre-procedure	All patients received IV infusion of 0.45% NaCl at 100 ml/h beginning 12 hours before, and continuing through the cardiac catheterization
				3	Anp	IV	ANP 50ug bolus then infusion 1ug/min in 0.45% NaCl at 100 ml/h, 2h, During CM administration After CM administration Other, as below, all patients received IVF starting 12 hours pre-procedure	All patients received IV infusion of 0.45% NaCl at 100 ml/h beginning 12 hours before, and continuing through the cardiac catheterization
				4	Mannitol	IV	Mannitol 15g/dl in 0.45 NaCl at 100 ml/h, 2h, During CM administration After CM administration Other, as below, all patients received IVF starting 12 hours pre-procedure	All patients received IV infusion of 0.45% NaCl at 100 ml/h beginning 12 hours before, and continuing through the cardiac catheterization

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Wolak, 2013[65]	NR	IA	Mean volume: Arm1: 115.5 ml Arm2: 119.0 ml Arm3: 105.7 ml	1	Continued ACE/ARB	NR	ACE and/or ARB treatment continued throughout study period. ACE/ARB dose determined by patient physician. Administration route not reported.	All patients given saline hydration for 12 hours before and 12 hours after image study, plus 600mg NAC twice daily 24 hours before and 24 hours after image study. Not reported whether oral or intravenous for saline or NAC.
				2	Short delay of ACE/ARB	NR	ACE and/or ARB stopped 24 hours prior to procedure and re-started immediately after. ACE/ARB dose determined by patient physician. Administration route not reported.	All patients given saline hydration for 12 hours before and 12 hours after image study, plus 600mg NAC twice daily 24 hours before and 24 hours after image study. Not reported whether oral or intravenous for saline or NAC.
				3	Long delay of ACE/ARB	NR	ACE and/or ARB stopped 24 hours prior to procedure and re-started 24 hours after. ACE/ARB dose determined by patient physician. Administration route not reported.	All patients given saline hydration for 12 hours before and 12 hours after image study, plus 600mg NAC twice daily 24 hours before and 24 hours after image study. Not reported whether oral or intravenous for saline or NAC.
XinWei, 2009[66]	Iodixanol, Iohexol	IA	Body weight (kg) x 5ml/serum creatinine.	1	Simvastatin 20	Oral	20mg/day from admission to the day before PCI, and then resumed simvastatin 20 mg/day for the following days, Up to 48h after procedure. Prior and After CM administration	All patients were hydrated with intravenous isotonic saline (0.9%) at a rate of 1 ml/kg body weight per hour for 6 to 12 hours before and 12 hours after coronary catheterization to achieve a urinary flow rate of
				2	Simvastatin 80	Oral	80mg/day from admission to the day before PCI, and then resumed simvastatin 20 mg/day for the following days. Up to 48h after procedure. Prior and After CM administration	
Yavari, 2014[67]	Iodixanol	IA	Mean Volume: Arm1: 185.88 ml, Arm2: 191.96 ml	1	0.9% IV Normal Saline	IV	0.9% Normal Saline, 1 ml/kg/h, 6 hour prior, during and up to 6 hour after procedure	
				2	0.9% IV Normal Saline + Oral Pentoxifyllline	Oral, IV	400 mg PO x 3 day Pentoxifylline., Day of procedure and Day after procedure	Also given 0.9% IV Normal Saline, 1 ml/kg/h at 6 hour prior, during and up to 6 hour after procedure

Evidence Table I-3. Interventions for studies comparing interventions to prevent development of CIN (continued)

Author, year	Contrast Medium	Contrast Administration	Dose, Duration, Volume	Arm	Intervention	Administration	Intervention: dose, duration temporal association to contrast	Other intervention details
Yin, 2013 [68]	Other description, Ultravist- nonionic, low- osmolality contrast medium	IA	Not specified, Not specified	1	No probucol	IV	0.9% isotonic saline(1ml/kg/h), 24 hours, After CM administration	After coronary intervention, all patients underwent hydration with intravenous isotonic saline (0.9%) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram After coronary intervention, all patients underwent hydration with intravenous isotonic saline (0.9%) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram per hour in the cases of overt heart failure) for 24 h.
				2	Probucol	Oral, IV	1000mg before procedure and 500mg twice daily after, before procedure and 3 days after procedure, Prior to CM administration After CM administration	After coronary intervention, all patients underwent hydration with intravenous isotonic saline (0.9%) at a rate of 1 ml per kilogram of body weight per hour (or 0.5 ml per kilogram

ACEI= Angiotensin Converting Enzyme Inhibitor, ANP=Atrial Natriuretic Peptide, AVH= Amlodipine Valsartan Hydration, b.i.d=Bi-daily, Bev=Beverage, CAG=Coronary Angiogram, Cc/hr= cubic centimeter per kilogram, CECT=Contrast Enhanced Computed Tomography, CM=Contrast Media, H=Hour, HD=Hemodialysis, hrs=hours, IA=Intrarterial, IOCM=Iso-Osmolar Contrast Media, IQR=Interquartile Range, IV=Intravenous, IVF=Intrvenous Fluid, LCA=Left Coronary Artery, LOCM=Low-Osmolar Contrast Media, Mcg/kg/min=microgram per kilogram per min, MD= Doctor of Medicine, mEq/l= milliequivalents per liter, Mg/dl=milligram per deciliter, Mg/kg/hour=milligram per kilogram per hour, Mg/kg=milligram per kilogram, Mg=milligram, mls=milliliters, mOsm/kg= milliosmoles per kilogram, N/A=Not Applicable, NAC=N-acetylcysteine, NaCl=Sodium Chloride, NaHCO3=Sodium Bicarbonate, NR=Not Reported, Osm=Omsolarity, p.o.=By Mouth, PCI=Percutaneous Coronary Intervention, PCWP=Pulmonary Capillary Wedge Pressure, POBID=By mouth twice daily, RCA=Right Coronary Artery, SB=Sodium Bicarbonate, SD=Standard Deviation, Ug/kg/min=microgram per kilogram per minute, VO=Vocal Order

Evidence Table I-4. Summary of studies of N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	Number randomized (Number analyzed if differerent)	Population	Age, years (or range of means¶)	No. female (%)§	Total follow-up	CM Route*	Definition of CIN*	Study limitations†
Allaqaband, 2002 [5]	IV 0.45% saline vs. oral NAC + IV 0.45% saline vs. IV IV fenoldopam + 0.45% saline +	126 (123)	CKD (SrCr ≥ 1.6 mg/dl or an estimated creatinine clearance ≤ 60 ml/min)	71	52 (42)	48 hours	LOCM IA	A2a	M
Baskurt, 2009[8]	IV normal saline vs. oral NAC + IV normal saline vs. Oral NAC + oral theophylline + IV normal saline	217	Moderate degree (stage 3) CKD (eGFR between 30 and 60 ml/min/1.73 m^2)	67	87 (40)	12 months	LOCM (Ioversol) IA	A2b	H
Briguori, 2004 [10]	Oral NAC + IV 0.45% saline vs. IV fenoldopam + IV 0.45% saline	192	CKD (stable SrCr ≥ 1.5 mg/dl and/or creatinine clearance < 60 mL/min)	68-69	29 (15)	48 hours	IOCM (Iodixanol), IA	A2b	M
Briguori, 2004[11]	Oral NAC single-dose (600 mg bid) + IV 0.45% saline vs. Oral NAC double-dose (1200 mg bid) + IV 0.45% saline	223	CKD (stable SrCr ≥table SrCr ed/or creatinine clearance <60 ml/min)	66-67	41 (18)	48 hours	Iobitriol IA	A2b	M
Briguori, 2007[12]	Oral NAC + IV normal saline vs. Oral NAC + IV NaHCO3 in dextrose and water vs Oral NAC + IV ascorbic acid + IV normal saline	351 (326)	CKD (SrCr ≥2.0 mg/dl and/or estimated GFR < 40 ml/min/1.72m^2	69-71	57 (17)	48 hours	Iodixanol IA	A1b	M
Brueck, 2013 [78]	IV normal saline + placebo vs. IV NAC + IV normal saline vs. IV ascorbic acid + IV normal saline	520 (499)	SrCr ≥ 1.3 mg/dl	74-75	181 (36)	72 hours	Iopromide (LOCM) IA	A2b	L
Castini, 2010[79]	IV normal saline vs. + IV normal saline vs. IV NaHCO3	156	SrCr ≥ 1.2 mg/dl	70-72	19 (12)	5 days	Iodixanol (IOCM) IA	A1b	M
Chen, 2008 [14]	If SrCr <1.5 mg/dL:No intravenous fluids vs. IV 0.45% saline. If SrCr ≥1.5 mg/dL, then NAC + IV 0.45% saline vs. NAC without intravenous fluids	936	Myocardial Ischemia, scheduled for percutaneous coronary intervention (PCI)	56-67	84	6 months	IOCM IA	A2a	H
Demir, 2008 [16]	IV normal saline vs. NAC + IV normal saline vs. misoprostol + IV normal saline + vs. theophylline+ IV normal saline vs. nifedipine + normal saline	97	Non-diabetic, no CKD	43-78	43 (44)	72 hours	Iomeprol, Iopamidol IV	A3b	H
Gunebakmaz, 2012[21]	normal saline vs. normal saline + nebivolol vs. NAC + normal saline	120	SrCr ≥ 1.2 mg/dl	64-66	38 (31)	5 days	Iopromide IA	A3b	H

Evidence Table I-4. Summary of studies N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of means[¶]	No. female (%)[§]	Total follow-up	CM Route*	Definition of CIN*	Study limitations†
Hafiz, 2012 [22]	IV normal saline with or without oral NAC vs. IV NaHCO3 in 5% dextrose in water with or without oral NAC	320	SrCr >1.6 mg/dl in non-diabetics and >1.4 mg/dl in diabetics or an estimated glomerular filtration rate (eGFR) of <50 ml/min/1.73 m^2	73	138 (43)	48 hours	LOCM IA	A3a	M
Heguilen, 2013 [25]	IV NaHCO3 vs. NAC + IV NaHCO3 vs. NAC + IV normal saline	133 (123)	Stable SrCr ≥1.25 mg/dl or estimated creatinine clearance > 45 ml/min, but SrCr must be ≤ 4.5 mg/dl	64-69	34 (25)	72 hours	Ioversal IA	A1b	M
Holscher, 2008[26]	IV normal saline + glucose vs. + hemodialysis IV normal saline +glucose vs. oral NAC + IV normal saline + g glucose	412	SrCr 1.3-3.5 mg/dl	67	68 (16.5)	30 days	Iopromide IA	A2b	H
Huber, 2006[27]	IV ttheophylline vs. IV NAC vs. IV theophylline + IV NAC	91	At least one risk factor for CIN; stable renal function	58.5	31 (34)	48 hours	Iomeprol (LOCM) IA and IV	See footnote ‡	M
Kinbara, 2010[29]	IV normal saline vs. + IV aminophylline + normal saline vs. NAC + normal saline	45	Stable coronary artery disease and stable SrCr	70-71	17 (37)	48 hours	Iopamidol IA	A2a	M
Kotlyar, 2005[34]	IV normal saline vs IV NAC 300mg in 5% dextrose + IV normal saline + vs. IV NAC 600mg in 5% dextrose + IV normal saline	65 (60)	Stable SrCr concentrations ≥0.13 mmol/l (1.47 mg/dl)	66-69	7 (11)	30 days	Iopromide IA	A2b	M
Kumar, 2014[36]	Oral NAC + IV Saline vs. Allopurinol + IV Saline	95	Coronary block	65	110 (22)	5 days	LOCM (Iohexol) IOCM (Iodixanol) IA	Oral	NR
Marenzi, 2006 [46]	IV normal saline + placebovs. standard-dose NAC (600 mg IV NAC before the procedure, then 600 mg twice a day for 48 h after the contrast) + normal saline vs. High-dose NAC + (1200 mg IV NAC before the contrast, then 1200 mg orally twice a day for 48 hours after) + IV normal saline	354	ST elevation acute myocardial infarction	62-62	50 (14)	NR	Iohexol IA	A1b	M
Ng, 2006 [50]	Oral NAC + IV normal saline vs. IV fenoldopam + IV normal saline	95 (84)	Stable renal disease, SrCr >1.2 mg/dl	68	24 (25)	72 hours	Only non-ionic LCOM or IOCM IA	A3a	M
Ozcan, 2007[80]	IV normal saline vs NAC + IV normal saline vs IV NaHCO3 in dextrose	264	SrCr > 1.2 mg/dl and ≤ 4 mg/dl	69	67 (25)	48 hours	Ioxaglate (LOCM) IA	A3a	H
Ozhan, 2010[52]	NAC + IV saline vs. NAC + atorvastatin + IV saline	130	No renal insufficiency (SrCr ≤ 1.5 and GFR ≥ 70 ml/min)	54-55	53 (41)	48 hours	Iopamidol IA	A3a	M

Evidence Table I-4. Summary of studies N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	N	Population	Age, range of means¶	No. female (%)§	Total follow-up	CM Route*	Definition of CIN*	Study limitations†
Ratcliffe, 2009 [54]	IV normal saline in 5% dextrose vs. NAC + IV normal saline in 5% dextrose vs. IV NaHCO3 in 5% dextrose vs. NAC + IV NaHCO3 in 5% dextrose	118 (78)	CKD and/or diabetes mellitus	66	31(40)	7 days	Iodixanol (IOCM) IA	A1a	H
Recio-Mayoral, 2007 [55]	Oral NAC post-contrast + IV normal saline vs. IV NAC pre- contrast oral NAC post-contrast+ IV sodium bicarbonate in 5% glucose and water	111	Patients with myocardial infarction treated with PCI or high-risk non-ST segment elevation acute coronary syndrome needing urgent revascularization (no GFR inclusion criteria other than the exclusion of dialysis patients)	65	34 (31)	7 days	Iomeprol (LOCM) IA	A2b	H
Reinecke, 2007 [56]	IV normal saline +5% glucose vs. one session of hemodialysis + IV normal saline + 5% glucose vs. oral NAC + IV normal saline + 5% glucose	424 (412)	SrCr 1.3-3.5 mg/dl	67-68	73 (17)	Mean follow-up: 553 days (63 to 1316 days)	Iopromide (IOCM) IA	A2b	H

%=percent; CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; dL=deciliter; eGFR=estimated glomerular filtration rate; IA=intrarterial; IV=intravenous; LOCM=low-osmolar contrast media; m^2=meter squared; mg=milligram; min=minute; ml=milliliter; mmol/l=millimole per liter; N=sample size; NAC=N-acetylcysteine; NaHCO3=sodium bicarbonate; NR=not reported; PCI=percutaneous coronary intervention; SrCr=serum creatinine

* CIN definitions: rise in serum creatinine relative to baseline: >25% (A1a); ≥25% (A1b); >0.5 mg/dl (A2a); ≥0.5 mg/dl (A2b); >25% or > 0.5 mg/dl (A3a); ≥25% or ≥0.5 mg/dl (A3b); ≥50% (A4) B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=medium risk of bias; H=high risk of bias
‡Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents, N Engl J Med 1994;331:1449–1450.
§ Percent females in entire study population
¶ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms if the mean age for the whole population is not reported

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Allaqaband, 2002 [5]	Arm1: IV 0.45% saline Arm2: NAC + IV 0.45% saline + Arm3: IV fenoldopam IV 0.45% saline +	Cr >0.5 mg/dl at 48 hours Arm1: 6/40 (15.3) Arm2: 8/45 (17.7) Arm3: 6/38 (15.7); P=0.919	Diabetics Cr >0.5 mg/dl at 48 hours Arm1: 3/6 (50) Arm2: 5/8 (62.5) Arm3: 4/6 (66.6); P=0.803 Use of Calcium channel antagonists Cr >0.5 mg/dl at 48 hours Arm1: 5/6 (83.3) Arm2: 3/8 (37.5) Arm3: 2/6 (33.3); P=0.150 Use of ACE inhibitors Cr >0.5 mg/dl at 48 hours Arm1: 3/6 (50) Arm2: 4/8 (50) Arm3: 2/6 (33.3); P=0.857	NR	Time point: NR 2 (1.62% of all participants)	NR	Three participants in Arm 3 were withdrawn because of hypotension. Other cardiac events NR.
Baskurt, 2009[8]	Arm1: IV normal saline Arm2: Oral NAC + IV normal saline Arm3: Oral NAC + oral theophylline + IV normal saline	Cr ≥0.5 mg/dl at 48 hours Arm1: -5/72 (6.9) Arm2: 7/73 (9.6) Arm3: 0/72 (0); P=0.033	NR	No deaths were observed in the 1-year follow-up of the participants who had developed CIN	0 (0%)	NR	No major adverse cardiac events were observed in the 1-year follow-up of the participants who had developed CIN

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Briguori, 2004 [10]	Arm 2: oral NAC + IV 0.45% saline Arm3 IV fenoldopam + IV 0.45% saline	SrCr ≥0.5 mg/dl at 48 hours Arm2: 4/97 (4.1) Arm3: 13/95 (13.7) OR 0.27 (95% CI: 0.08-0.85) P=0.019	Baseline SrCr > 2.5 mg/dL SrCr ≥0.5 mg/dl at 48 hours Arm2: 1/9 (11.0) Arm3: 5/11 (45.5); P=0.095 Diabetes SrCr ≥0.5 mg/dl at 48 hours Arm2: 3/49 (6.1) Arm3: 4/49 (8.2); P=0.72 LVEF <40% SrCr ≥0.5 mg/dl at 48 hours Arm2: 0/10 (0) Arm3: 4/13 (13.3); P=0.23 LVEF ≥40% SrCr ≥0.5 mg/dl at 48 hours Arm2: 4/87 (4.5) Arm3: 9/72 (12.5); P=0.085 Diabetes and LVEF < 40% SrCr ≥0.5 mg/dl at 48 hours Arm1: 0/9 (0) Arm2: 0/7 (0)	One of 95 (1.0%) participants in Arm 3 experienced in-hospital death.	At 48 hours Arm2: 0/97 (0) Arm3: 1/95 (1.1); P=NR	Arm2: 2.9 (2.7) Arm3: 5.0 (10); P=0.049	Two of 95 participants (2.1%) in Arm 3 had severe hypotension.

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Briguori, 2004[11]	Arm2: Oral NAC single-dose (600 mg bid) + IV 0.45% saline Arm3: Oral NAC double-dose (1200 mg bid) + IV 0.45% saline	Cr ≥0.5 mg/dl at 48 hours or need for dialysis Arm2: 12/109 (11) Arm3: 4/114 (3.5) OR 0.29 (95% CI: 0.09-0.94) P=0.038	Diabetics Renal function deterioration occurred in: Arm2: 4/47 (2.1) Arm3: 1/47 (2.1); P = 0.36 Left ventricular ejection fraction < 40% Renal function deterioration occurred in: Arm2: 4/22 (18.2) Arm3: 1/16 (6.3); P=0.37	NR (No apparent deaths because all participants had lab drawn at 48 hours)	0 (0)	Length of hospitalization Arm2: 2.6 (0.9) Arm3: 2.2 (0.6); P=0.018	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Briguori, 2007[12]	Arm2: Oral NAC + IV normal saline Arm3: Oral NAC + IV NaHCO3 in dextrose and water Arm4: Oral NAC + IV ascorbic acid + IV normal saline	Increase in SrCr ≥25% at 48 hours Arm2: 11/111 (9.9) Arm3: 2/108 (1.9) Arm4: 11/107 (10.3); P=0.010 Cr ≥0.5 mg/dl At 48 hours Arm2: 12/111 (10.8) Arm3: 1/108 (0.9) Arm4: 12/107 (11.2); P=0.026	Odds Ratio (95% CI) compared to Arm2: Diabetics Arm3: 0.6 (0.42-0.86) Arm4: 1.73 (0.59-5.10) No diabetes Arm3: 0.45 (0.36-0.56) Arm4: 0.21 (0.02-1.86) Other subgroups are reported in Figure 3	NR It is inferred that there were no death (all participants are accounted for)	Arm2: 1 (0.9) Arm3: 1 (0.9) Arm4: 4 (3.8); P=NR	NR	NR
Brueck, 2013[78]	Arm1: IV normal saline + placebo Arm2: IV NAC + IV normal saline Arm3: IV ascorbic acid + IV normal saline	Increase in SrCr ≥0.5 mg/dL at 72 hours Arm1: 62/193 (32.1) Arm2: 53/192 (27.6) Arm3: 24/98 (24.5); Arm1 vs Arm2: P=0.20 Arm1 vs Arm3: P=0.11	Diabetes Cr ≥0.5 mg/dL at 72 hours: Arm1: 36/102 (35.0) Arm2: 24/86 (28.4) Arm3: 14/48 (29.8) Arm1 vs. Arm2: P=0.65Arm1 vs. Arm3: P=0.62 SrCr ≤ 1.4 at baseline CIN at 72 hours: Arm1: 33.7% Arm3: 10.6%; P =0.0048 SrCr > 1.4 mg/dL at baseline CIN at 72 hours: Arm1: 30.9% Arm3: 37.3%; P = 0.14	NR	0(0)	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Castini, 2010[79]	Arm1: IV normal saline Arm2: NAC + IV normal saline +Arm3: IV NaHCO3	Increase in SrCr ≥25% within 5 days, but author provided data a 48 hours (personal communication): At 48 hours: Arm1: 4/51 (8) Arm2: 8/53 (17) Arm3: 5/52 (14); P=NR At 5 days: Arm1: 7/51 (14) Arm2: 9/53 (17) Arm3: 7/52 (14); P=0.85 Increase in SrCr ≥0.5 mg/dl : 48 hours Arm1: 4/51 (8) Arm2: 5/53 (9) Arm3: 4/52 (8); P=NR At 5 days: Arm1: 4/51 (8) Arm2: 5/53 (9) Arm3: 6/52 (12); P=0.82	NR	NR	0(0)	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Chen, 2008 [14]	If Sr Cr < 1.5 mg/dl Arm1: No IV fluids Arm2: IV 0.45% saline If SrCr ≥ 1.5 mg/dl: Arm3: Oral NAC without IV fluids Arm4: Oral NAC + IV 0.45% saline	Increase in SrCr >0.5 mg/dl at 48 hours Arm1: 23/330 (6.97) Arm2: 22/330 (6.67) Arm3: 64/188 (34.04) Arm4: 40 (21.28); P<0.001 Arm1 vs. Arm2 P>0.05 Arm3 vs. Arm4 P<0.01	NR	Death rates were reported by creatinine groups, but were not categorized by treatment arm.	The incidence of continuous veno-venous hemofiltration initiation was reported by creatinine group, but was not categorized by treatment arm.	NR	The overall incidence of arrhythmias and stroke were reported by creatinine group, but not be treatment arm.
Demir, 2008 [16]	Arm1: IV normal saline Arm2: NAC + IV normal saline Arm3: Misoprostol + IV normal saline Arm4: Theophylline + IV normal saline Arm5:Nnifedipine +IV normal saline	Increase in SrCr ≥25% or ≥0.5 mg/dl within 72 hours Arm1: 0/20 (0) Arm2: 1/20 (5) Arm3: 0/20 (0) Arm4: 4/20 (20) Arm5: 0/17 (0); P=NR	NR	NR	NR	NR	NR
Gunebakmaz, 2012[21]	Arm1: IV normal saline Arm2: Nebivolol + IV normal saline Arm3: NAC + IV normal saline	Increase in SrCr ≥25% and/or or ≥0.5 mg/dl at 72 hours Arm1: 11/40 (27.5) Arm2: 8/40 (20.0) Arm3: 9/40 (22.5); P=0.72	NR	NR	NR	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Hafiz, 2012 [22]	Arm1: IV normal saline with or without oral NAC Arm2: IV NaHCO3 in 5% dextrose in water without or without oral NAC	Increase in SrCr >25% or >0.5 mg/dl at 48 hours Arm1: 19/161 (11.8) Arm2: 14/159 (8.8); P=>0.05	without NAC Cr >25% or >0.5 mg/dl at 48 hours Arm1: 11/80 (13.8) Arm2: 6/79 (7.6); P=>0.05 without NAC Cr >25% or >0.5 mg/dl at 48 hours Arm1: 8/81 (9.9) Arm2: 8/80 (10.0); P=>0.05 Age (increasing years) Cr >25% or >0.5 mg/dl at 48 hours OR: 1.05 (95% CI: 1.02-1.08); P=0.001 Gender (female) Cr >25% or >0.5 mg/dl at 48 hours OR: 0.49 (95% CI: 0.21-1.13); P=0.095 OR: 3.42 (95% CI: 1.46-7.98); P=0.005 ACE inhibitors Cr >25% or >0.5 mg/dl at 48 hours OR: 0.1.12 (95% CI: 0.51-2.50); P=0.775	At 48 hours Arm1: 0/161 (0) Arm2: 0/159 (0); P=NR	NR	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Hafiz, 2012 [22] (continued)			Higher baseline Cr level Cr >25% or >0.5 mg/dl at 48 hours OR: 0.64 (95% CI: 0.35-1.19); P=0.161 Diabetes Cr >25% or >0.5 mg/dl at 48 hours OR: 1.57 (95% CI: 0.69-3.35); P=0.281 Contrast volume >3ml/kg Cr >25% or >0.5 mg/dl at 48 hours OR: 1.10 (95% CI: 1.00-1.20); P=0.038 GFR SrCr >25% or >0.5 mg/dl at 48 hours OR: 0.99 (95% CI: 0.98-1.01); P=0.435 Anemia Cr >25% or >0.5 mg/dl at 48 hours OR: 1.97 (95% CI: 0.42-9.29); P=0.390 Diuretics Cr >25% or >0.5 mg/dl at 48 hours OR: 3.42 (95% CI: 1.46-7.98); P=0.005				

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Heguilen, 2013 [25]	Arm1: IV NaHCO3 Arm2: NAC + IV NaHCO3 Arm3: NAC + IV normal saline	Increase in SrCr ≥ 25% at 72 hours Arm1: 15/42 (35.7) Arm2: 3/43 (6.98) Arm3: 6/38 (15.8); P<0.01	Acute myocardial infarction Cr ≥25% at 72 hours OR: 0.36 (95% CI: 0.08-1.54); P=0.17 Hypertension Cr ≥25% at 72 hours OR: 2.31 (95% CI: 0.40-13.31); P=0.35 Left ventricular dysfunction Cr ≥25% at 72 hours OR: 0.66 (95% CI: 0.12-3.53); P=0.63 NAC use Cr ≥25% at 72 hours OR: 0.18 (95% CI: 0.04-0.72); P=0.016 Contrast volume Cr ≥25% at 72 hours OR: 0.10 (95% CI: 0.99-1.02); P=0.10	NR	NR	NR	NR
Holscher, 2008[26]	Arm1: IV normal saline with 5% glucose Arm2: IV normal saline with 5% glucose +hemodialysis Arm3: Oral NAC + IV normal saline with 5% glucose	Increase in SrCr ≥0.5 mg/dl at 72 hours Arm1: 10/139 (7.2) Arm2: 22/134 (16.4) Arm3:6/139 (4.3) P=0.68	NR	NR by arm, but there were 73 deaths overall within the follow-up period	NR	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Huber, 2006[27]	Arm1: theophylline Arm2: NAC Arm3: theophylline + NAC	Based on prior definition (see summary table) at 48 hours Arm1: 1/51 (2) Arm2: 6/50 (12) Arm3: 2/49 (4); P=<0.001 Arm1 vs. Arm2 P=0.47 Arm2 vs. Arm3 p=0.146 Arm1 vs. Arm3 p=0.53	SrCr > 1.5 mg/dl Arm1: 0/12 (0) Arm2: 5/11 (45) Arm3: 1/14 (7) Arm1 vs Arm3: P=0.345	At 12 days Arm1: 3/51 (5.9) Arm2: 1/50 (2.0) Arm3: 0/49 (0); P=NR	1 patient required dialysis, no other details	NR	NR
Kinbara, 2010[29]	Arm1: IV normal saline Arm2: IV aminophylline + normal saline Arm3: NAC + IV normal saline	Increase in SrCr >0.5 mg/dl at 48 hours Arm1: 4/15 (26.7) Arm2: 0/15 (0) Arm3: 0/15 (0); P=0.0109	NR	NR	NR	NR	NR
Kotlyar, 2005[34]	Arm1: normal saline Arm2: NAC 300mg + normal saline + dextrose Arm3: NAC 600mg + normal saline + dextrose	Increase in SrCr ≥ 0.044 mmol/l (≥ 0.5 mg/dl at 48 hours Arm1: 0/19 (0) Arm2: 0/20 (0) Arm3: 0/21 (0); P=NR	NR	One patient died during the catheterization (not related to study protocol)	Chronic reduction in renal function at 30 days Arm1: 2/19 (11) Arm2: 4/20 (20) Arm3: 2/21 (10); P=0.66	NR	NR
Kumar, 2014[36]	Arm2: Oral NAC + IV Saline Arm2: Allopurinol + IV Saline	Definition NR Arm1: 18 Arm2: 0 P=NR	NR	NR	NR	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Marenzi, 2006 [46]	Arm1: placebo + IV normal saline Arm2: standard-dose NAC+ IV normal saline Arm3: high-dose NAC+ IV normal saline	Increase in SrCr ≥ 25% at 72 hours Arm1: 39/119 (33) Arm2: 17/115 (15) Arm3: 10/118 (8); P=<0.001 Increase in SrCr ≥0.5 mg/dl at 72 hours Arm1: 22/119 (18) Arm2: 7/115 (6) Arm3: 4/118 (3); P=<0.001	CrCl ≤60 ml/min Cr >25% at 72 hours Arm1: (43) Arm2: (27) Arm3: (19); P=0.25 CrCl>60 ml/min Cr >25% at 72 hours Arm1: (29) Arm2: (10) Arm3: (5); P=0.25 LVEF ≤40% Cr >25% at 72 hours Arm1: (63) Arm2: (33) Arm3: (23); P=0.71 LVEF >40% Cr >25% at 72 hours Arm1: (24) Arm2: (11) Arm3: (5); P=0.71	Time point NR Arm1: 13/119 (11) Arm2: 5/115 (4) Arm3: 3/118 (3); P=0.007	Time point NR Arm1: 6/119 (5) Arm2: 2/115 (2) Arm3: 1/118 (1); P=0.14	NR	Cardiogenic shock Arm1: 12/119 (10) Arm2: 6/115 (5) Arm3: 8/118 (7); P=0.35 High-rate atrial fibrillation Arm1: 10/119 (8) Arm2: 4/115 (3) Arm3: 10/118 (8); P=0.,22 Cardiopulmonary resuscitation, ventricular tachycardia, or ventricular fibrillation Arm1:17/119 (14) Arm2: 12/115 (10) Arm3: 8/118 (7); P=0.17 High-degree conduction disturbances Arm1: 10/119 (8) Arm2: 6/115 (5) Arm3: 8/118 (7); P=0.63 Acute pulmonary edema requiring mechanical ventilation Arm1: 9/119 (8) Arm2: 2/115 (2) Arm3: 2/118 (22); P=0.03

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Ng, 2006 [50]	Arm1: Oral NAC + IV normal saline Arm2: IV fenoldopam + IV normal saline	Increase in SrCr >25% or ≥ 0.5 mg/dl at 72 hours Arm1: 5/44 (11.4) Arm2: 8/40 (20.0); P=0.4	At 72 hours: There were no differences in the incidence of CIN in the subgroups that were analyzed (diabetics vs non-diabetics, SrCr > 1.7 and 2 mg/dL, gender, age > 70 years, and contrast volume of at least 150 and 200 mL.)	NR	NR	NR	NR
Ozcan, 2007[80]	Arm1: IV normal saline Arm2: NAC + IV normal saline Arm2: IV NaHCO3 in dextrose Arm3:	Increase in SrCr >25 or 0.5 mg/dL at 48 hours Arm1: 12/88 (13.6) Arm2: 11/88 (12.5) Arm3: 4/88 (4.5) Arm1 vs. Arm2: RR 0.95 (95% CI: 0.37-2.17) P=0.82 Arm1 vs. Arm3: RR 0.30 (95% CI: 0.09-0.97) P=0.036 Arm2 vs. Arm3: RR 0.33 (95% CI: 0.10-1.09) P=0.059	NR	NR	At 48 hours Arm1: 1/88 (1.14) Arm2: 0/88 (0) Arm3: 1/88 (1.14); P=NR	NR	Congestive heart failure at 48 hours Arm1: 0/88 (0) Arm2: 0/88 (0) Arm3: 0/88 (0); P=NR
Ozhan, 2010[52]	Arm2: NAC + IV saline Arm3: NAC + atorvastatin+ IV saline	Increase in SrCr >25% or >0.5 mg/dl at 48 hours Arm1: 7/70 (10) Arm2: 2/60 (3.33); P=0.135	NR	NR	NR	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Ratcliffe, 2009 [54]	Arm1: IV normal saline in 5% dextrose Arm2: NAC + IV normal saline in 5% dextrose Arm3: IV NaHCO3 in 5% dextrose Arm4: NAC + IV NaHCO3 in 5% dextrose	SrCr >25% at 72 hours Arm1: 1/15 (7) Arm2: 1/21 (5) Arm3: 2/19 (11) Arm4: 1/23 (4); P=0.863	There were no significant differences between the subgroups (renal insufficiency and/or diabetes mellitus) in CIN incidence; P=0.313	NR	NR	NR	NR (Authors report that there were no serious adverse events.)
Recio-Mayoral, 2007 [55]	Arm1: Oral NAC post–contrast + IV normal saline Arm2: IV NAC pre-contrast oral NAC post-contrast+ IV sodium bicarbonate in 5% glucose and water	Primary endpoint: SrCr ≥ 0.5 mg/dl within 72 hours Arm1: 12/55 (21.8) Arm2: 1/56 (1.8); P=0.0009 OR 0.065 (95% CI, 0.008 to 0.521, P = 0.01) for Arm2. SrCr >25% within 72 hours Arm1: 17/55 (30.9) Arm2: 1/56 (1.8); P<0.0001 SrCr > 50% within 72 hours Arm1: 8/55 (14.5) Arm2: 0/56 (0); P=0.003	NR	At 7 days Arm1: 4/55 (7.3) Arm2: 1/56 (1.8); P=0.21	At 7 days Arm1: 3/55 (5.5) Arm2: 1/56 (1.8); P=0.36	NR	Acute pulmonary edema/heart failure (during catheterization): Arm1: 2 (3.6) Arm2: 1 (1.8); P=0.62

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Reinecke, 2007 [56]	Arm1: IV normal saline +5% glucose Arm2: One session of hemodialysis + IV normal saline + 5% glucose Arm3: Oral NAC + IV normal saline + 5% glucose	SrCr ≥0.5 mg/dl At 24 hours Arm1: 8/137 (5.8) Arm2: 7/135 (5.2) Arm3: 4/140 (2.9); P=0.461 Within 72 hours Arm1: 7/115 (6.1) Arm2: 18/113 (15.9) Arm3: 6/114 (5.3); P=0.008 At 30-60 days Arm1: 6/125 (4.8) Arm2: 6/118 (5.1) Arm3: 4/129 (3.1); P=0.704	Incidence of CIN (SrCr ≥ 0.5 mg/dl) in the following subgroups: Diabetics: Time point NR Arm1: (13.3) Arm2: (18.4) Arm3: (9.7); P=0.577 Non-Diabetics: Time point NR Arm1: (3.5) Arm2: (14.7) Arm3: (3..6); P=0.007 SrCr <2mg/dl Time point NR Arm1: (5.7) Arm2: (14.0) Arm3: (2.9); P=0.009 SrCr ≥2mg/dl Time point: NR Arm1: (10.0) Arm2: (2.05) Arm3: (17.3); P=0.570 Stage 3 CKD (GFR 30-59 ml/min) Cr >0.5 mg/dl Time point: 72 hours Arm1: (5.9) Arm2: (16.0) Arm3: (4.1); P=0.007	In-hospital Arm1: 1/NR (0.7) Arm2: 3/NR (2.2) Arm3: 1/NR (0.7); P=0.427 30-Day Arm1: 3/NR (2.2) Arm2: 3/NR (2.2) Arm3: 1/NR (0.7); P=0.540 Long-Term mortality, deaths per 100 patient-years (median long-term follow-up: 553 days, with range 63 to 1316 days), Arm1: 9.7 Arm2: 13.1 Arm3: 9.9; P=0.582	In-hospital Time point: NR Arm1: 1/NR (0.7) Arm2: 2/NR (1.5) Arm3: 1/NR (0.7); P=0.762	NR	NR

Evidence Table I-5. Summary of all outcomes reported in studies comparing N-acetylcysteine versus other interventions for the prevention of contrast-induced nephropathy (continued)

*Divide SrCr presented as micromol/liter by 88.4 to obtain mg/ml; %=percent; AMI=acute myocardial infarction; CI=confidence interval; Cr=creatinine; CrCl=creatinine clearance; CIN=contrast induced nephropathy; dL=deciliter; IV=intravenous; LVEF=Left Ventricular Ejection Fraction; mg=milligram; ml/kg=milliliter per kilogram; ml/min=milliliter per minute; N=sample size; NAC=N-acetylcysteine;; NaHCO3=sodium bicarbonate;; NR=not reported; OR=odds ratio; P=p-value; RRT=renal replacement therapy; SD=standard deviation; SrCr: serum creatinine

*n/N refers to number of events divided by number at risk.

Evidence Table I-6. Summary of studies comparing sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population included	Age, range of means§	No. female (%)‡	Mean followup	CM route*	Definition of CIN*	Study limitations†
Cho, 2010[15]	IV Normal Saline vs. IV Normal Saline + NaHCO3 vs. Oral fluids vs. Oral fluids + NaHCO3	91	CKD (Cr ≥1.1 mg/dl or eGFR ≤60 ml/min)	77-81	45 (49)	72 hours	LOCM (Isoversol) IA	A3	M
Klima, 2012[30]	IV Normal Saline vs LT NaHCO3 vs. ST NaHCO3	258	>93 umol/L Cr for women and >117 umol/L Cr for men or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2	69-81	92(36)	48 hours	LOCM, IOCM IA or IV	A3	M
Kooiman, 2014[33]	No hydration vs. IV 1.4% NaHCO3	138	CKD (eGFR < 60 mL/min/1.73m^2)	70	69 (50.0)	2 months	LOCM (Iopromide, Iobitridol) IOCM (Iodixanol) IA	A3	M
Pakfetrat, 2009[53]	IV Normal Saline + dextrose vs. NaHCO3 + dextrose vs. IV Normal Saline + Acetazolamide	286	General	58-59	111 (39)	48 hours	IOCM (Iodixanol) IA	RIFLE criteria	M

CIN=contrast induced nephropathy; Cr=creatinine; eGFR=estimated glomerular filtration rate; H=high risk; IA=Intrarterial; IOCM=iso-osmolar contrast media; IV=intravenous; L=low risk; LOCM=low osmolar contrast media; LT=long term; M=moderate risk; Mg/dl=milligram per deciliter; Mmol/l=millimole per liter; N=sample size; NaCl=sodium chloride; NaHCO3=sodium bicarbonate; ST=short-term; Umol/l=micromole per liter

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-7. Summary of all outcomes reported in studies comparing sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Cho, 2010[15]	Arm1: IV Normal Saline Arm2: IV Normal Saline + NaHCO3 Arm3: Oral fluids Arm4: Oral fluids + NaHCO3	SrCr ≥25% or ≥ 0.5 mg/dl At 72 hours Arm1: 6/27 (22) Arm2: 2/21 (9.5) Arm3: 1/22 (4.5) Arm4: 1/21 (4.8) Arm1 vs. Arm2 p=0.784 Arm1 vs. Arm3 p=0.617 Arm1 vs. Arm4 p=0.342 Arm2 vs. Arm3 p=0.835 Arm2 vs. Arm4 p=0.525	NR	At 72 hours Arm1: 0/27 (0) Arm2: 0/21 (0) Arm3: 0/22 (0) Arm4: 0/21 (0) p=NR	NR	Arm1: 4.18 Arm2: 4.09 Arm3: 4.36 Arm4: 6.9 p=0.657	NR
Klima, 2012[30]	Arm1: IV Normal Saline Arm2: LT NaHCO3 Arm3: ST NaHCO3	SrCr ≥ 0.5 mg/dl At 48 hours Arm1: 1/89 (1) Arm2: 7/87 (8) Arm3: 6/82 (7) p=0.03 SrCr ≥25% At 48 hours Arm1: 1/89 (1) Arm2: 8/87 (9) Arm3: 8/82 (10) p=0.02	NR	NR	NR	NR	NR

Evidence Table I-7. Summary of all outcomes reported in studies comparing sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Kooiman, 2014[33]	Arm1: No hydration Arm2: IV 1.4% NaHCO3	SrCr ≥25% or ≥ 0.5 mg/dl At 48-96 hours Arm1: 6/65 (9.2) Arm2: 5/70 (7.1) p<0.001 RR: 1.29 (95% CI: 0.41-4.03) p=NR	NR	NR	Need for Dialysis At 2 months Arm1: 0/65 (0) Arm2: 0/70 (0) p=NR	NR	NR
Pakfetrat, 2009[53]	Arm1: IV Normal Saline Arm2: IV NaHCO3 + dextrose Arm3: IV Normal Saline + Acetazolamide	Rifle criteria At 48 hours Arm1: 16/96 (16.6) Arm2: 4/96 (4.2) Arm3: 5/94 (5.3) p=0.04	NR	NR	NR	NR	At 48 hours Arm1: 0/96 (0) Arm2: 0/96 (0) Arm3: 0/94 (0) p=NR

%=percent; CI=confidence interval; CIN=contrast induced nephropathy; IV=intravenous; IVF=intravenous fluid; LT=long term; Mg/dl=milligram per deciliter; N=sample size; NaHCO3=sodium bicarbonate; NR=not reported;; P=P-value; RR=relative risk; RRT=renal replacement therapy; SD=standard deviation; SrCr=serum creatinine; ST=short term; Umol/l=micomole per liter

*n/N refers to number of events divided by number at risk.

Evidence Table I-8. Summary of studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population included	Age, range of means‖	No. female (%)¶	Mean followup	CM Route	Definition of CIN*	Study limitations†
Briguori, 2007[12]	IV Normal Saline + Oral NAC vs. IV NaHCO3 + Oral NAC vs. IV Normal Saline + Oral Ascorbic Acid + Oral NAC	326	CKD with stable Cr at 2.0 mg/dL and/or eGFR rate < 40 ml/min	71-70	57 (17)	7 days	IOCM (Iodixanol) IA	A1	M
Briguori, 2011[13]	IV NaHCO3 in dextrose + Oral NAC vs. RenalGuard: IV (IV Normal Saline+ IV NAC + IV furosemide)	292	CKD (eGFR ≤30 ml/min)	76	101 (34)	1 month	IOCM (Iodixanol) IA	Increase in Cr >0.3mg‡	L
Heguilen, 2013[25]	IV NaHCO3 + dextrose v IV NaHCO3 + Oral NAC +dextrose v IV Normal Saline + Oral NAC + dextrose	133	Stable Cr $\geq$ 1.25 mg/dl, or estimated CrCl <45 ml/min	64-67	31 (25)	48-72 hours	LOCM (Ioversol) IA	A1	M
Heng, 2008[81]	IV NaHCO3 + Oral Placebo vs. IV NaHCO3 + Oral NAC	60	Chronic renal failure, GFR < 56 ml/min, stable Cr concentrations	71-72	13 (21)	48 hours	IOCM (Iodixanol), LOCM (Iomeprol) IA	A1	H
Maioli, 2008[43]	IV Normal Saline + Oral NAC vs. IV NaHCO3 + Oral NAC	502	CKD, CrCl < 60 ml./min	74	206 (41)	10 days	IOCM (Iodixanol) IA	A1 §	L
Ratcliffe, 2009[54]	IV Normal Saline vs. IV Normal Saline + Oral/IV NAC +dextrose vs. IV NaHCO3 +dextrose vs. IV NaHCO3 + Oral/IV NAC + dextrose	78	Renal insufficiency, Cr Men >132.6 mg/dL Women >114.9 mg/dL and/or diabetes	64-68	31 (39)	7 days	IOCM (Iodixanol) IA	A1	H
Staniloae, 2009[82]	IV NaHCO3 vs. Oral NAC + IV NaHCO3	414	Moderate-to-severe chronic kidney disease with eGFR of 20-59ml/min per 1.73 m^2	149 (36)	71	7 Days	IOCM (Iodixanol), LOCM (Iopamidol) IA	A2	M

Evidence Table I-8. Summary of studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy and other outcomes (continued)

CIN=contrast induced nephropathy; CM=contrast media; Cr=creatinine; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; IA=intrarterial; IV=intravenous; mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NaCl=sodium chloride; NaHCO3=sodium bicarbonate; vs.=versus

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4). B: >25% reduction in creatinine clearance.
† Study limitations: L=low risk of bias; M=moderate risk of bias; H =high risk of bias
‡ increase of serum creatinine >25% was secondary outcome
§CIN outcomes also assessed at 48 hours.
¶ Percent females in entire study population
║ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-9. Summary of all outcomes reported in studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)*	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)	Need for RRT, n/N (%)	Prolonged hospitalization, mean days (SD)	Cardiac events, n/N (%)
Briguori, 2007[12]	Arm2: IV Normal Saline+ Oral NAC Arm3:IV NaHCO3 + Oral NAC Arm4: IV Normal Saline + Oral Ascorbic Acid + Oral NAC	Cr >25% At 48 hours Arm2: 11/111 (9.9) Arm3: 2/108 (1.9) Arm4: 10/107 (10.3) p=0.010 Arm2 vs. Arm3 p=0.019 Arm2 vs. Arm4 p=1.00 Cr change >0.5mg Arm2: 12/111 (10.8) Arm3: 1/108 (0.9) Arm4: 12/107 (11.2) p=0.026 Arm2 vs. Arm3 p<0.003 Arm2 vs. Arm4 p>0.05	NR	NR	Requiring temporary dialysis At 7 days Arm2: 1/111 (0.9) Arm3: 1-108 (0.9) Arm4: 4/107 (3.8) p=NR	NR	NR
Briguori, 2007[12] (continued)		eGFR increase >25% Arm2: 10/111 (9.2) Arm3: 1/108 (0.9) Arm4: 12/107 (11.2) p=0.018 Arm2 vs. Arm3 p<0.009 Arm2 vs. Arm4 p>0.05					

Evidence Table I-9. Summary of all outcomes reported in studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)*	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)	Need for RRT, n/N (%)	Prolonged hospitalization, mean days (SD)	Cardiac events, n/N (%)
Briguori, 2011[13]	Arm1: IV NaHCO3 in dextrose + Oral NAC Arm2: RenalGuard: IV (IV Normal Saline+ IV NAC + IV furosemide)	Cr >0.3mg At 48 hours Arm1: 30/146 (20.5%) Arm2: 16/146 (11%) p=0.025 Cr >25% At 48 hours Arm1: 19/146 (13) Arm2: 4/146 (2.7) p=NR Cr >50% At 48 hours Arm1: 11/146 (7.5) Arm2: 1/146 (0.7) p=NR Cr >0.5mg At 48 hours Arm1: 22/146 (15) Arm2: 9/146 (6) p=NR	CR> 0.3mg at 48 hours GFR <30 Arm1: 20/68 (29.5) Arm2: 11/74 (15) p=NR CI-AKI Risk score >11 At 48 hours Arm1: 11/78 (14) Arm2: 5/72 (7) p=NR	Death At 1 month Arm1: 6/146 (4.1) Arm2: 6/146 (4.1) p=1.0	Need for RRT At 1 month Arm1: 7/146 (4.8) Arm2: 1/146 (0.7) p=0.03	NR	Acute pulmonary edema At 1 month Arm1: 1/146 (0.7) Arm2: 3/146 (2.1) p=0.62
Heguilen, 2013[25]	Arm1: IV NaHCO3 + dextrose Arm2: IV NaHCO3 + Oral NAC +dextrose Arm3: IV Normal Saline + Oral NAC+dextrose	Cr >25% At 48-72 hours Arm1: 15/42 (35.7) Arm 2: 3/43 (7.0) Arm3: 6/38 (15.8) p<0.001	NR	At 48-72 hours Arm1 vs. Arm2 vs. Arm3 p=NS	At 48-72 hours Arm1 vs. Arm2 vs. Arm3 p=NS	At 48-72 hours Arm1 vs. Arm2 vs. Arm3 p=NS	NR

Evidence Table I-9. Summary of all outcomes reported in studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)*	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)	Need for RRT, n/N (%)	Prolonged hospitalization, mean days (SD)	Cardiac events, n/N (%)
Heng, 2008[81]	Arm1: IV NaHCO3 + Oral Placebo Arm2: IV NaHCO3 + Oral NAC	Cr >44µmol/L At 48 hours Arm1: 2/32 (6.3) Arm2: 0/28 (0) p=0.49 Cr >25% At 48 hours Arm1: 2/32 (6.3) Arm2: 1/28 (3.5) p=1.0 Decrease in GFR by 5ml/min At 48 hours Arm1: 3/32 (9.3) Arm2: 2/28 (7.1) p=1.0	NR	NR	Need for RRT At 48 hours Arm1: 0 (0) Arm2: 0 (0) p=NR	NR	Congestive heart failure At 48 hours Arm1: 0/32 (0) Arm2: 1/28 (3.6) p=NR
Maioli, 2008[43]	Arm2: IV Normal Saline + Oral NAC Arm3: IV NaHCO3 + Oral NAC	Cr >25% At 48 hours Arm2: 25/250 (10.0) Arm3: 38/252 (15.1) p=0.09 Cr >25% At 5 days Arm2: 29/250 (11.5) Arm3: 25/252 (10) p=0.60	NR	NR	Need for hemofiltration At 10 days Arm2: 1/250 (0.4) Arm3: 1/252 (0.4) p=NR	NR	NR

Evidence Table I-9. Summary of all outcomes reported in studies comparing N-acetylcysteine plus sodium bicarbonate versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)*	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)	Need for RRT, n/N (%)	Prolonged hospitalization, mean days (SD)	Cardiac events, n/N (%)
Ratcliffe, 2009 [54]	Arm1: IV Normal Saline Arm2: IV Normal Saline + Oral/IV NAC +dextrose Arm3: IV NaHCO3 +dextrose Arm4: IV NaHCO3 + Oral/IV NAC + dextrose	Cr >25% At 72 hours Arm1: 1/15 (7) Arm2: 1/21 (5) Arm3: 2/19 (11) Arm4: 1/23 (4) p=0.86	NR	NR	NR	NR	NR
Staniloae, 2009 [82]	Arm1: IV NaHCO3 Arm2: IV NaHCO3 + Oral NAC	Cr >25% At 45-120 hours Arm1: 26(10.6) Arm2: 20(11.9 p=0.75 eGFR >25% At 45-120 hours Arm1: 21(8.5) Arm2: 12(7.1) p=0.71 Cr >0.5mg At 45-120 hours Arm1: 16(6.5) Arm2: 7(4.2) p=0.38	NR	NR	NR	NR	NR

%=percent; CIN=contrast induced nephropathy; CKD=chronic kidney disease; CM=contrast media; F=female; IA=Intrartieral; IOCM=iso-osmolar contrast media; IV=intravenous; LOCM=low osmolar contrast media; mg/dl=milligram per deciliter; N=sample size; NAC=N-acetylcysteine; NormS=normal saline; vs.=versus; Cr=creatinine

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-10. Adverse events in studies comparing of N-acetylcysteine plus sodium bicarbonate versus other interventions

Author, Year	Adverse events
Briguori, 2007[12]	NR
Briguori, 2011[13]	Other: Mortality; Deaths at 1 month post procedure; Acute pulmonary edema; at 1 month post procedure
Heguilen, 2013[25]	NR
Heng, 2008[81]	Two participants (one from each arm) developed diarrhea.
Maioli, 2008[43]	Heart failure: 5 patients had acute cardiac failure resulting in death; Anaphalaxis; Infective multi organ failure: 1 patient had this event resulting in death
Ratcliffe, 2009[54]	No serious adverse events from any of the medications given or from the procedure itself
Staniloae, 2009[82]	NR

NR=not reported

Evidence Table I-11. Summary of studies comparing diuretics versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population	Age, Range of means§	Mean followup	Procedure	CM	Definition of CIN*	Study limitations†
Marenzi, 2012[47]	Normal saline vs. Normal saline + furosemide (furosemide bolus up to 50mg)	170	Inclusion eGFR <60 ml/min/1.73 m^2 CKD stages 3-4 NYHA < IV	61-90	72 hours	Urgent or elective coronary angiography w/ or w/o PCI	LOCM Iomeprol	A3	M
Pakfetrat, 2009[53]	Normal saline vs. bicarbonate vs. Normal saline + acetazolamide	286	All patients undergoing coronary intervention	46–68	48 hours	Coronary angiography w/ or w/o PCI	IOCM Iodixanol	Rifle criteria	M
Solomon, 1994[60]	0.45% saline vs. 0.45% saline + furosemide vs. 0.45% saline + mannitol (furosemide infusion up to 80mg)	78	Cr >1.6 mg/dl/ eGFR <60 ml/min/1.73 m^2	50-78	48 hours	Coronary angiography	LOCM Iopentol	A2	L

CKD=Chronic Kidney Disease; CIM=Contrast induced nephropathy; CM=Contrast media; Cr=creatinine; CrCl=Creatinine Clearance; eGFR=estimated glomular filtration rate; HOCM=high-osmolar contrast media; IOCM=iso-osmolar contrast media; LOCM=low-osmolar contrast media; NYHA=New York health association; PCI=Percutaneous coronary intervention; RCT=Randomized Controlled Trial

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡RIFLE criteria: (at 48 hours), Scr increase x 1.5 or GFR decrease > 25% from baseline + urine output <5ml/kg/h x 6h
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-12. Summary of all outcomes reported in studies of diuretics versus other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN n/N (%)*	Clinical events n/N (%)	Mortality n/N (%)	Need for RRT n/N (%)	Cardiac events, n/N (%)
Marenzi, 2012[47]	Arm 1: Normal saline Arm 2:Normal saline + furosemide	Overall Arm1: 15/83 (18%) Arm2: 4/87 (4.6%) P=0.005, RR=0.29 CIN in patients with elective procedures Arm1: 5/52 (10%) Arm2: 2/48 (4%) P=0.44, RR=0.42 CIN in patients with urgent procedures Arm1: 10/31 (32%) Arm2: 2/39 (5%) P=0.003, RR=0.16	In-hospital complications Arm1: 7 (8%) Arm2: 15 (18%) P=0.052 Acute pulmonary edema Arm1: 5 (6%) Arm2: 10 (12%) P=0.15 Acute myocardial infarction Arm1: 0 (-) Arm2: 1 (1.2%) P =0.30 Atrial fibrillation Arm1: 1 (1.1%) Arm2: 2 (2.4%) P=0.53	In-hospital death Arm1: 1 (1.1%) Arm2: 3 (4%) P=0.29	Arm1: 3 (4%) Arm2: 1 (1%) P=0.29	AMI Arm1: 1/83 (1.2) Arm2: 0/87 (0) P=0.30
Pakfetrat, 2009[53]	Arm 1: Normal saline Arm 2: bicarbonate Arm 3: Normal saline + acetazolamide	Risk Arm1: 12 (12.5%) Arm2: 4 (4.2%) Arm3: 5 (5.3%) P=0.04 Injury Arm1: 3 (1%) Arm2: 0 (-) Arm3: 0 (-) P=0.05 Failure Arm1: 1 (0.3%) Arm2: 0 (-) Arm3: 0 (-) P=0.37	No events	No events	No events	

Evidence Table I-12. Summary of all outcomes reported in studies of diuretics versus other interventions for the prevention of contrast-induced nephropathy (continued)

Author, year	Comparison	Incidence of CIN n/N (%)*	Clinical events n/N (%)	Mortality n/N (%)	Need for RRT n/N (%)
Solomon, 1994[60]	Arm 1: 0.45% saline Arm 2: 0.45% saline + furosemide Arm 3: 0.45% saline. + mannitol	Arm1: 3/28 (11%) Arm2: 10/25 (40%) 7/25 (28%) P=0.05 CIN in diabetic (n=13) Arm1: 2 /14 (14%) Arm2: 6/14 (43%) Arm3: 5/13 (38%) P =NS CIN in non-diabetic (n=7) Arm1: 1/14 (7%) Arm2: 4/11 (36%) Arm3: 2/12 (17%) P=NS	Length of hospitalization + 4 days in CIN patients	NR	Arm1: 0/28 Arm2: 1/25 Arm3: 0/25

AMI=acute myocardial infarction; CHF=chronic heart failure; CIN=contrast induced nephropathy; NR=not reported; RR=relative risk; RRT=renal replacement therapy

*n/N; number of events/population at risk (patients in arm)

Evidence Table I-13. Summary of the characteristics of studies comparing vasoactive agents with other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparators	N	Population	Age, range of means‡	Procedure / CM	Definition of CIN*	Hydration and duration	Vasodilator dose and duration	Study limitations†
Allaqaband, 2002[5]	0.45% saline vs. 0.45% saline + fenoldopam vs. 0.45% saline + NAC	123	SrCr ≥ 1.6 mg/dl	70-71	Cardiovascular interventions LOCM	A2	Saline 0.45%, 24 hours (12 hours before-12 hours after)	NAC 600 mg PO X2 12 h before-12 hours after (total 1200mg) Fenoldopam 0.1mcg/kg/min infusion for 8 hours (4 hours before, 4 hours after CM)	M
Briguori, 2004[10]	0.45% saline + fenoldopam vs. 0.45% saline + NAC	192	SrCr >1.5 mg/dl or CrCl <60ml/min	68-69	Coronary and/or peripheral angiography IOCM	A2	Saline 0.45% 24 hours (12 hours before-12 hours after)	NAC 1200 mg PO bid x 2 days (the day before and the day of the procedure) (total 4800mg) Fenoldopam 0.1mcg/kg/min infusion starting 1 hour before CM and for 12 hours after.	M
Demir, 2008[16]	Normal saline vs. Normal saline + nifedipine vs Normal saline + NAC vs Normal saline + misoprostol vs. Normal saline + theophylline	97	Stable renal disease SrCr >1.2mg/dl	43-77	Computed tomography LOCM	A3	Saline 0.9% 2000ml	Nifedipine 30 mg/day for 5 days starting 3 days before the procedure	H
Gunebakmaz, 2012[21]	Normal saline vs. Normal saline+ nevibolol vs. Normal saline + NAC	120	SrCr ≥ 1.2mg/dl	53-66	Cardiovascular interventions IOCM	A3	Saline 0.9% 1ml/kg/h infusion for 82h (6 hours before, 12 hours after)	Nevibolol 5mg day for 4 days starting 2 days before procedure	H
Li, 2011[39]	Normal saline vs. Normal saline+ benazepril	114	Mild or moderate CKD CrCl ≥60ml/min ≤89 ml/min	52-72	Coronary interventions LOCM	A3	Saline 0.9% 1ml/kg/h infusion for 12h (6 hours before, 6 hours after)	Benazepril 10mg/day, 3 days, Prior to CM administration	H

Evidence Table I-13. Summary of the characteristics of studies comparing vasoactive agents with other interventions for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparators	N	Population	Age, range of means‡	Procedure / CM	Definition of CIN*	Hydration and duration	Vasodilator dose and duration	Study limitations†
Li, 2014 [40]	IV Normal Saline vs. IV Normal Saline + IV Prostaglandin E1	163	CIN Risk Score >11	65	PCI LOCM	A3	0.9% saline IV for routine hydration	20 ng/kg/min IV prostaglandin E1, beginning1 hour prior to CM administration for 6 hours	H
Liu, 2013[41]	Statin vs. Statin + Alprostadil	156	Mild to moderat kidney disease (eGFR 60-89 ml/min/1.73 m2)	65	Coronary angiography or PCI IOCM	A3	IV Normal saline, 1-1.5 ml/kg/h, 3-12 h pre and 6-24 hours post procedure	40 mg/day statin (see Arm1) + 20 mcg/day IV alprostadil, 1 day prior and 6 days post procedure	H
Ng, 2006[50]	Normal saline + fenoldopam vs. Normal saline + NAC	95	SrCr >1.5 mg/dl or CrCl <60ml/min	57-80	Coronary angiography IOCM, LOCM	A3	Saline 0.9% 1ml/kg/ starting 1-2 hours before continuing 6-12 hours after	NAC 600 mg PO bid x 2 days (the day before and the day of the procedure) (total 2400mg) Fenoldopam 0.1mcg/kg/min infusion for 8 hours (2 hours before, 6 hours after CM)	M
Oguzhan, 2013[51]	Normal saline vs. Normal saline + amlodipin-valsartan	90	SrCr <2.1 mg/dl	62-66	Coronary arteriography and ventriculography LOCM	A3	Saline 0.9% 24 hours (12 hours before, 12 hours after)	Amlodipine-valsartan 5/160mg x3 (24h before the procedure-the day of the procedure and 24 hours after)	H
Talati, 2012[62]	Intra renal fenoldopam +hydration (not specified) vs. matched control (NAC) + hydration (not specified)	52	Coronary procedurees	69	Cardiovascular interventions IOCM	A3	No mention of hydration protocol	NAC 1200 mg 4 doses PO (2 before, 2 after) (total 4800mg) Fenoldopam 0.1-0.4mcg/kg/min intrarenal	H
Wolak, 2013[65]	Continued ACE/ARB vs. Short delay ACE/ARB vs Long delay ACE/ARB	94	General	65	Coronary arteriography CM not reported	NR	Saline solution not specified, for 12 hours prior and after image study	Dose determined by physician	H

CIN=contrast induced nephropathy; CM=contrast media; IOCM-ios-osmolar contrast media; Cr=creatinine; LOCM=low-osmolar contrast media; NA=not applicable; NAC=n-acetylcysteine; PO=per os; SrCr=serum creatinine

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4). B: >25% reduction in creatinine clearance.
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-14. Summary of the outcomes of studies comparing vasoactive agents versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	Incidence of CIN n/N (%)*	Length of hospitalization , mean days	Mortality n/N (%)	Need for RRT n/N (%)
Allaqaband, 2002[5]	Arm 1: 0.45% saline Arm 2: 0.45% saline + fenoldopam Arm 3: 0.45% saline + NAC	Overall (N=20) Arm1: 15.3% Arm2: 15.7% Arm3: 17.7% P=0.919 CIN in diabetes (Y/N) Arm1: 3/3 Arm2: 5/3 Arm3: 4/2 P=0.813	NR	NR	2 of the 20 patients developing CIN required HD (not reported by group)
Briguori, 2004[10]	Arm 1: 0.45% saline + fenoldopam Arm 2: 0.45% saline + NAC	Overall Arm1: 13/95 (13.7%) Arm2: 4/97 (4.1%) P=0.019, OR=0.27 (0.08-0.85) CIN in diabetic patients Arm1: 5/11 (45%) Arm2: 1/9 (11%) P=0.095 CIN in patients with Cr >2.5 Arm1: 27/135 (20%) Arm2: 11/140 (7.9%) P=0.005	Length of hospitalization Arm1: 5.0 +/- 10 Arm2: 2.9 +/- 2.7 P=0.049	Arm1: 1 (1.1%) Arm2: 0 (-)	Arm1: 1 (1.1%) Arm2: 0 (-)
Demir, 2008[16]	Arm 1: Normal saline vs. Arm 2: Normal saline + nifedipine Arm 3: Normal saline + NAC Arm 4: Normal saline + misoprostol Arm 5: Normal saline + theophylline	Arm1: 0/20 (-) Arm2: 0/17 (-) Arm3: 1/20 (5%) Arm4: 0/20 (-) Arm5: 4/20 (20%	No difference in length of hospitalization	NR	Arm1: 0 Arm2: 0 Arm3: 0 Arm4: 0 Arm5: 0
Gunebakmaz, 2012[21]	Arm 1: Normal saline vs. Arm 2: Normal saline+ nevibolol Arm 3: Normal saline + NAC	Arm1: 11 (27.5%) Arm2: 8 (20%) Arm3: 9 (22.5% P=0.72	NR	NR	NR
Li, 2011[39]	Arm 1: Normal saline Arm 2: Normal saline+ benazepril	Arm1: 9.7% Arm2: 3.5% P=0.506	NR	NR	NR

Evidence Table I-14. Summary of the outcomes of studies comparing vasoactive agents versus other interventions for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN n/N (%)*	Length of hospitalization , mean days	Mortality n/N (%)	Need for RRT n/N (%)
Li, 2014 [40]	Arm1: IV Normal Saline Arm2: IV Normal Saline + IV Prostaglandin E1	At 3 days Arm1: 9/81 (11.1) Arm2: 3/82 (3.7) p<0.05 OR: 0.387 (95% CI: 0.212-0.787) p=0.013	NR	NR	NR
Liu, 2013[41]	Arm1: Statin Arm2: Statin + Alprostadil	At 48 hours Arm1: 6/80 (7.5) Arm2: 5/76 (6.6) p=NS	NR	NR	NR
Ng, 2006[50]	Arm 1: Normal saline + fenoldopam Arm 2: Normal saline + NAC	Overall Arm1: 8/40 (20%) Arm2: 5/44 (11.4%) P=0.4 No association after adjusting for diabetes, CHF and gender P=0.3	Length of hospitalization + 4 days in CIN patients	NR	NR
Oguzhan, 2013[51]	Arm 1: Normal saline Arm 2: Normal saline + amlodipin-valsartan	Arm1: 3 (6.7%) Arm2: 8 (17.8%) P=0.197	NR	NR	0 0
Talati, 2012[62]	Arm 1: Intra renal fenoldopam +hydration (not specified) Arm 2: matched control (NAC) + hydration (not specified)	Arm1: 6/52 (11.5%) Arm: 16/52 (30%) P=0.012 RR 0.38 95%CI 0.16-0.88)	Length of hospitalization in CIN patients Arm1: 5.7 +/- 4.6 Arm2: 8.1 +/- 6.1 P=0.39	Arm1: 0 Arm2: 1 P=0.52	Arm1: 0 Arm2: 3 P=0.52
Wolak, 2013[65]	Arm1: Continued ACE/ARB Arm2: Short delay ACE/ARB Arm3: Long delay ACE/ARB	NR	NR	NR	NR

CHF=congestive heart failure; CI=confidence interval; CIN=contrast induced nephropathy; Cr=creatinine; HD=hemodialysis; NAC=n-acetylcysteine; RRT=renal replacement therapy

*n/N; number of events/population at risk (patients in arm)

Evidence Table I-15. Adverse events in studies comparing vasoactive agents versus other interventions for the prevention of contrast induced nephropathy

Author, Year	Adverse events
Allaqaband,2002[5]	Other: Hypotension; Fenoldopam reaction. Definition not reported
Briguori,2004[10]	Other: Hypotension; Allergic reaction; skin rash and vomiting
Demir,2008[16]	NR
Gunebakmaz, 2012[21]	NR
Li, 2011[39]	NR
Li, 2014 [40]	NR
Liu, 2013[41]	Major event (cardiac death, non-fatal MI, ischemic stroke): Arm1: 8, Arm2: 3 ESRD, revascularization, CABG, CHF, pulmonary edema, need for permanent pacing: Arm1: 18, Arm2: 7 AE incidence within 6 months of the procedure were significantly lower in the aloprostadil group (p=0.035).
Ng, 2006[50]	No patient had any adverse event in any arm
Oguzhan, 2013[51]	NR
Talati, 2012[62]	Other: Hypotension; NR
Wolak, 2013[65]	NR

NR=not reported

Evidence Table I-16. Summary of the characteristics and outcomes of studies comparing antioxidants versus hydration for the prevention of contrast-induced nephropathy

Author, year	Comparisons	N	Procedure / CM	Definition of CIN*	Hydration and duration	Agent dose and duration	Study limitations†
Firouzi, 2012[18]	Normal saline vs. Normal saline + pentoxifylline	286	Coronary angioplasty LOCM	A3	Saline 0.45% 1ml/kg/ 12 hours (6 hours before, 6 hours after)	400mg PO 3 x day for 48 hours starting 24 hours before CM	H
Kimmel, 2008[28]	0.45% saline+ placebo vs. 0.45% saline +NAC vs. 0.45% saline + zinc	54	Coronary angiography w/ or w/o PCI LOCM	A3	Saline 0.45% 1ml/kg/ 24 hours (12 hours before, 12 hours after)	NAC 600 mg PO bid x 2 days (total 2400mg) Zinc 60mg PO 24 hours before CM	M
Li, 2009[38]	Normal saline vs. Normal saline + probucol	205	Coronary angiography w/ or w/o PCI LOCM	A3	Saline 0.9% 1ml/kg/ 12 hours after	Probucol 500mg PO before procedure-then 500mg PO bid for 3 days	H
Ludwig, 2011[42]	Normal saline + placebo vs. Normal saline + MESNA	100	Coronary and peripheral angiography-CT LOCM	A1	Saline 0.9% 1000 ml before and 500 ml after CM	MESNA 1600mg IV (in 500 ml saline) immediately before procedure	L
Shehata, 2014[59]	IV Normal Saline + Oral NAC vs IV Normal Saline + Oral NAC + Oral Trimetazidine	100	PCI IOCM	A2	IV Normal Saline started 12 hours before up to 24 hours after.	35mg Trimetazidine twice daily for 72 hours, starting 48 hours before procedure	M
Yavari, 2014[67]	IV Normal Saline vs IV Normal Saline + Oral Pentoxifylline	199	PCI IOCM	A1	0.9% Normal Saline, 1 ml/kg/h, 6 hour prior, during and up to 6 hour after procedure	400 mg PO x 3 day Pentoxifylline., Day of procedure and Day after procedure	M
Yin, 2013[68]	Arm1: No probucol Arm2: Probucol	204	Primary or urgent coronary angioplasty	A3	Saline 0.9% 1mlm/kg/ 24 hours	Probucol 1000mg before procedure and 500mg twice daily after	M

Bid=*bis in die*; CIN=contrast induced nephropathy; CM=contrast media; CT=computerized tomography; def=definition; IV=intravenous; LOCM=low-osmolar contrast media; MESNA= sodium 2-mercaptoethanesulfonate; ml/kg/hours=milliliter per kilogram per hour; Ml=milliliter; N=sample size; NAC=N-acetylcysteine; NS=non-significant; p=p-value; PCI=percutaneous coronary intervention; PO=*per os*; Vs=versus; w/=with; w/o=without

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡n/N; number of events/population at risk (patients in arm)

Evidence Table I-17. Summary of the characteristics and outcomes of studies comparing either misoprostol or angiotensin blockers versus hydration for the prevention of contrast-induced nephropathy

Author, year	Comparisons	N	Procedure / CM	Definition of CIN*	Hydration and duration	Agent dose and duration	Study limitations†
Demir, 2008[16]	Normal saline vs. Normal saline + misoprostol vs. Normal saline + NAC vs. Normal saline + theophylline vs. Normal saline + nifedipine	97	Computed tomography LOCM	A3	Saline 0.9% 2000ml	Misoprostol 200mg, bid, 3 days prior, day of, 1 day post procedure	H
Rosenstock, 2008[57]	Naïve to angiotensin blockade vs. Continue angiotensin blockade during and after procedure vs Discontinue angiotensine blockade morning of procedure and 24 hrs after procedure	283	Coronary angiography	A3	Dose and duration not reported	Dose and duration not reported	H

bid=*bis in die*; CIN=contrast induced nephropathy; CM=contrast media; Hrs=hours; LOCM=low-osmolar contrast media; mg=milligram; ml=millimeter; N=total sample size; NAC=N-acetylcysteine; vs=versus

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡n/N; number of events/population at risk (patients in arm)

Evidence Table I-18. Summary of all outcomes reported in studies comparing antioxidants versus hydration for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Firouzi, 2012[18]	Arm1: Normal saline Arm2: Normal saline + pentoxifylline	Arm1: 20/146 (13.7) Arm2: 12/140 (8.5) P=0.17	NR	48 hours Arm1: 0/146 (0) Arm2: 0/140 (0) P=NR	48 hours Arm1: 0/146 (0) Arm2: 0/140 (0) P=NR	NR	NR
Kimmel, 2008[28]	Arm1: 0.45% saline+ placebo Arm2: 0.45% saline +NAC Arm3: 0.45% saline + zinc	Arm1: 1/17 (6) Arm2: 1/19 (5) Arm3: 2/18 (11) P=NS	CIN def: A1 Arm1: 2/17 (12) Arm2: 1/19 (5) Arm3: 3/18 (17) P=NS	NR	NR	NR	NR
Li, 2009[38]	Arm1: Normal saline Arm2: Normal saline + probucol	Arm1: 15/103 (14.56) Arm2: 8/102 (7.84) P=0.13	NR	NR	NR	NR	NR
Ludwig, 2011[42]	Arm1: Normal saline + placebo Arm2: Normal saline + MESNA	Arm1: 7/49 (14) Arm2: 0 (0) P=0.005	NR	NR	NR	NR	NR
Shehata, 2014[59]	Arm2: IV Normal Saline + Oral NAC Arm3: IV Normal Saline + Oral NAC + Oral Trimetazidine	Increase in SrCr >25% or >0.5 mg/dl at 72 hours Arm2: 14/50 (28) Arm3: 6/50 (12) p<0.05	NR	NR	Need for hemodialysis At 72 hours Arm2: 0/50 (0) Arm3: 0/50 (0) p=NR At 10 days Arm2: 0/50 (0) Arm3: 0/50 (0) p=NR	NR	Incidence of acute pulmonary edema At 48 hours Arm2: 3/50 (6) Arm3: 1/50 (2) p=NR
Yavari, 2014[67]	Arm1: IV Normal Saline Arm2: IV Normal Saline + Oral Pentoxifylline	Increase in SrCr >25% at 48 hours Arm1: 6/102 (5.9) Arm2: 6/97 (6.2) p=0.92	Diabetics Arm1: 2/23 (8.7) Arm2: 2/27 (7.4) p=0.86 Hypertensive Arm1: 4/49 (8.7) Arm2: 2/40 (5) p=0.68	48 hours Arm1: 0/102 (0) Arm,2: 0/97 (0) p=NR	48 hours Arm1: 0/102 (0) Arm,2: 0/97 (0) p=NR	NR	NR

Evidence Table I-18. Summary of all outcomes reported in studies comparing antioxidants versus hydration for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Yin, 2013[68]	Arm1: No probucol Arm2: Probucol	At 72 hours Arm1: 23/108 (21.3) Arm2: 4/96 (4.2) P<0.001	NR	NR	NR	NR	NR

CIN=contrast induced nephropathy; Hrs=hours; MESNA= sodium 2-mercaptoethanesulfonate; n=number of patients with event; N=total sample size; NAC=N-acetylcysteine; NR=not reported; NS=not significant; P=p-value; RRT=renal replacement therapy; SD=standard deviation

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡n/N; number of events/population at risk (patients in arm)

Evidence Table I-19. Summary of all outcomes reported in studies comparing either misoprostol or angiotensin blockers versus hydration for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)	Mortality, n/N (%)*	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Demir, 2008[16]	Arm1: Normal saline Arm2: Normal saline + misoprostol Arm3: Normal saline + NAC Arm4: Normal saline + theophylline Arm5: Normal saline + nifedipine	Arm1: 0/20 (0) Arm2: 0/20 (0) Arm3: 1/20 (5) Arm4: 4/20 (20) Arm5: 0/17 (0)	NR	NR	NR	NR	NR
Rosenstock, 2008[57]	Arm1: Naïve to angiotensin blockade Arm2: Continue angiotensin blockade during and after procedure Arm3: Discontinue angiotensine blockade morning of procedure and 24hrs after procedure	At 72 hours Arm1: 4/63 (6.3) Arm2: 7/113 (6.2) Arm3: 4/107 (3.7) P=0.66	NR	NR	72 hours Arm1: 0/63 (0) Arm2: 0/113 (0) Arm3: 1/107 (0) P=NR	NR	NR

CIN=contrast induced nephropathy; Hrs=hours; MESNA= sodium 2-mercaptoethanesulfonate; n=number of patients with event; N=total sample size; NAC=N-acetylcysteine; NR=not reported; NS=not significant; P=p-value; RRT=renal replacement therapy; SD=standard deviation

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡n/N; number of events/population at risk (patients in arm)

Evidence Table I-20. Summary of characteristics of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other

Author, year	Comparison	N	Population included	Age, range of means‡	Sex, n female (%)	Mean follow-up	CM Route*	Definition of CIN*	Risk of bias†
Bader, 2004[7]	Saline infusion before and after procedure vs. Saline infusion during procedure	39	Cr level between 0.6 and 1.2 mg/dl	64-65	7 (18)	48 hours	LOCM (Iohexol, Iopromide) IA	Decrease in GFR of >50% from the baseline GFR within 48 hours	H
Brar, 2014[9]	IV Normal Saline vs. LVEDP-guided IV hydration	396	eGFR >60 ml/min/1.73 m^2	71	151 (38)	6 months	LOCM (Ioxilan) IA	A3	L
Chen, 2008[14]	No hydration vs. IV 0.45% saline vs. Oral NAC + no hydration vs. IV Saline 0.45% + Oral NAC	936	Myocardial ischemia	60-63	149 (16)	6 months	IOCM IA	A2	H
Cho, 2010[15]	IV Normal Saline vs. IV NaHCO3 vs. Oral hydration vs. Oral hydration + oral NaHCO3	91	CR ≥1.1 mg/dL or CrCl ≤60 mL/min	77-80	31 (34)	5 days	LOCM (Isoversol) IA	A3	M
Koc, 2012[31]	NAC + high-volume Normal Saline vs. High-volume NAC + high-volume Normal Saline vs. Standard-volume Normal Saline	220	CR ≥1.1 mg/dL or CrCl ≤60 mL/min	62-65	50 (22)	48 hours	LOCM (Iohexol) IA	A3	H
Kong, 2012[32]	IV Normal Saline vs. oral hydration	120	Coronary artery disease	54-57	53 (44)	6 months	LOCM (Iopromide) IA	A3	H
Krasuski, 2003[35]	Normal Saline vs. 0.45% Saline + dextrose	63	Moderate renal insufficiency	68-69	63 (17)	48 hours	NR	A2	H
Lawlor, 2007[37]	IV Normal Saline vs. IV Normal Saline + Oral NAC vs. Oral hydration + oral NAC	78	CrCl <50 mL/min	NR	24 (30)	48 hours	CM type NR IA	A1	H
Maioli, 2011[44]	No hydration vs. Late IV Normal Saline vs Early IV NaHCO3	450	STEMI	64-66	120 (26)	48 hours	IOCM (Iodixanol) IA	A3	M
Manari, 2014[45]	IV Normal Saline vs. High-dose IV Normal Saline vs. IV NaHCO3 vs. High-dose IV NaHCO3	592	STEMI meeting inclusion criteria	65	149 (25)	1 year	IOCM (Iodixanol) IA	A3	M
Marron, 2007[48]	IV Normal Saline vs. IV 0.45% Saline	71	General	64-68	23 (32)	30 days	IOCM (Iodixanol) IA	A1	H
Mueller, 2002[49]	IV Normal Saline vs. IV 0.45% Saline + 5% glucose	1383	General	64	354 (26)	30 days	LOCM IA	A2	H
Trivedi, 2003[63]	IV Normal Saline vs. Oral hydration	53	Coronary artery disease	67-68	1 (1.8)	48 hours	LOCM IA	A2	H

GFR=glomular filtration rate; IA=intra-arterial; IOCM=iso-osmolar contrast media; ISO=isotonic; Cr=creatinine; CrCl=creatinine clearance IV=intravenous; LOCM-low-osmolar contrast media; NAC=N-acetyl cysteine.; NaCl=sodium chloride; NaHCO3=sodium bicarbonate; NR=not reported; STEMI=ST segment elevation MI

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4). B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Bader, 2004[7]	Arm1: Saline infusion before and after procedure Arm2: Saline infusion during procedure	eGFR ≥50% At 48 hours Arm1: 1/19 (5.3) Arm2: 3/20 (20) All arms p=0.605	Diabetes At 48 hours Arm1: 0/6 (0) Arm2: 1/4 (25) No Diabetes At 48 hours Arm1: 1/13 (7.7) Arm2: 2/16 (12.5)	NR	Time point: NR Arm1: 0/19 (0) Arm2: 0/20 (0) p=NR	NR	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Brar, 2014[9]	Arm1: IV Normal Saline Arm2: LVEDP-guided IV hydration	SrCr ≥25% At 1-4 days Arm1: 27/172 (15.7) Arm2: 23/178 (6.7) RR: 0.43 (95% CI: 0.22-0.82) p=0.008 SrCr ≥ 0.5 mg/dl At 1-4 days Arm1: 11/172 (6.4) Arm2: 5/178 (2.8) RR: 0.44 (95% CI: 0.16-0.1.24) p=0.11 SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 28/172 (16.3) Arm2: 12/178 (6.7) 0.41 (95% CI: 0.22-0.79) p=0.005	No Diabetes SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 8/82 (9.8) Arm2: 1/87 (1.1) RR: 0.12 (95% CI: 0.02-0.92) p=NR Diabetes SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 20/90 (22.2) Arm2: 11/91 (12.1) RR: 0.54 (95% CI: 0.28-1.07) p=NR Male SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 11/101 (10.9) Arm2: 4/116 (3.9) RR: 0.32(95% CI: 0.10-0.96) p=NR Female SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 17/71 (23.9) Arm2: 8/62 (12.9) RR: 0.54 (95% CI: 0.25-1.16) p=NR	At 30 days Arm1: 3/200 (1.5) Arm2: 0/196 (0) p=0.25 At 6 months Arm1: 8/200 (4) Arm2: 1/196 (0.5) p=0.037	At 30 days Arm1: 3/200 (1.5) Arm2: 1/196 (0.5) p=0.62 At 6 months Arm1: 4/200 (2) Arm2: 1/196 (0.5) p=0.37	NR	At 30 days Arm1: 4/200 (2) Arm2: 1/196 (0.5) p=0.37 At 6 months Arm1: 13/200 (6.5) Arm2: 4/196 (2) p=0.29

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Brar, 2014[9] (continued)	Arm1: IV Normal Saline Arm2: LVEDP-guided IV hydration		NAC user SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 12/97 (17.9) Arm2: 4/66 (6.1) RR: 0.34 (95% CI: 0.11-1.0) p=NR NAC non-user SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 16/105 (15.2) Arm2: 8/112 (7.1) RR: 0.47 (95% CI: 0.21-1.05) p=NR Contrast >100ml SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 20/93 (21.5) Arm2: 8/94 (8/5) RR: 0.40 (95% CI: 0.18-0.85) p=NR Contrast <100ml SrCr ≥25% or ≥ 0.5 mg/dl At 1-4 days Arm1: 8/79 (10.1) Arm2: 4/84 (4.8) RR: 0.47 (95% CI: 0.15-1.50) p=NR				
Chen, 2008[14]	Arm1: Non hydration Arm2: IV 0.45% saline Arm3: Oral NAC + non hydration Arm4: IV Saline 0.45% + Oral NAC	SrCr ≥ 0.5 mg/dl At 48 hours Arm1: 23/330 (6.97) Arm2: 22/330 (6.67) Arm3: 64/188 (34.04) Arm4: 40/188 (21.28) p<0.001	NR	NR	NR	NR	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Cho, 2010[15]	Arm1: IV Normal Saline Arm2: IV NaHCO3 Arm3: Oral hydration Arm4: Oral hydration + oral NaHCO3	SrCr ≥25% At 72 hours Arm1: 6 (22.2) Arm2: 2 (9.5) Arm3: 2 (9.1) Arm4: 1 (4.7) Arm1 vs. Arm2 P=0.78 Arm1 vs. Arm3 P=0.62 Arm1 vs. Arm4 P=0.34 Arm2 vs. Arm3 P=0.84 Arm2 vs. Arm4 P=0.53 Arm3 vs. Arm4 P=0.66	NR	NR	NR	Arm1: 4.2 (4.5 Arm2: 4.1 (4.0) Arm3: 4.4 (6.5) Arm4; 6.9 (9.4) p=0.66	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Koc, 2012[31]	Arm1: Standard-dose IV Normal Saline Arm2: IV NAC plus high-dose IV Normal Saline Arm3: High-dose IV Normal Saline	SrCr ≥25% At 48 hours Arm1: 2 (2.5) Arm2: 13 (16.3) Arm3: 6 (10.0) p=0.012	Age >70 At 48 hours Arm1: 0 (0) Arm2: 6 (18.9) Arm3: 3 (14.3) P=0.14 LVEF <40 At 48 hours Arm1: 1 (3.6) Arm2: 1 (5.6) Arm3: 2 (15.0) P=0.50 Contrast dose >100ml At 48 hours Arm1: 2 (4.2) Arm2: 9 (18.0) Arm3: 4 (9.1) P=0.07 Diabetes At 48 hours Arm1: 2 (6.7) Arm2: 3 (14.3) Arm3: 3 (12.5) P=0.63 Baseline CrCl<50 At 48 hours Arm1: 1 (4.8) Arm2: 8 (33.3) Arm3: 3 (30.0) P=0.03	NR	NR	NR	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Kong, 2012 [32]	Arm1: IV Normal Saline Arm2: Pre and post oral hydration Arm3: Post oral hydration	SrCr ≥25% At 48-72 hours Arm1: 2/40 (5) Arm2: 3/40 (7.5) Arm3: 2/40 (5) p=0.86	NR	In-hospital At 4 days Arm1: 0/40 (0) Arm2: 0/40 (0) Arm3: 0/40 (0) p=NR	NR	NR	NR
Krasuski, 2003[35]	Arm1: IV 0.45% Saline Arm2: IV Normal Saline	SrCr >0.5mg/dl At 48 hours Arm1: 0/26 (0) Arm2: 4/37 (11) p=0.136	CrCl <50ml/min At 48 hours Arm1: 0/17 (0) Arm2: 3/20 (15) p=0.234	NR	Permanent dialysis At 48 hours Arm1: 0/26 (0) Arm2: 2/37 (5.4) p=0.503	NR	NR
Lawlor, 2007[37]	Arm1: IV Normal Saline + placebo Arm2: IV Normal Saline + oral NAC Arm3: Oral hydration + oral NAC	SrCr ≥25% At 48 hours Arm1: 2 (8.0) Arm2: 2 (8.0) Arm3: 2 (7.0) p=0.99	Baseline SrCr >200 µmol/L At 48 hours Arm1: 2(40.0) Arm2: 1(20.0) Arm3: 2 (33.0) P=0.78	NR	NR	NR	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Maioli, 2011[44]	Arm1: No hydration Arm2: Llate IV Normal Saline Arm3: Early IV NaHCO3	SrCr ≥25% At 3 days Arm1: 41/150 (27.3) Arm2: 34/150 (22.7) Arm3: 18/150 (12.0) P=0.001	SrCr ≥ 25% High to very high CIN risk >11 At 3 days Arm1: 18/52 (34.6) Arm2: 14/46 (46) Arm3: 11/45 (24.4) P=0.28 eGFR <60 At 3 days Arm1: 10/34 (29.4) Arm2: 12/46 (26.1) Arm3: 6/40 (15.0) P=0.14 Age >75 years At 3 days Arm1: 11/29 (37.9) Arm2: 15/36 (41.7) Arm3: 8/38 (21.1) P=0.12 Diabetes At 3 days Arm1: 10/34 (29.4) Arm2: 11/31 (35.5) Arm3: 5/31 (16.1) P=0.24	In-hospital At 3 days Arm1: 8/150 (5.3) Arm2: 5/150 (3.3) Arm3: 3/150 (2.0) P=0.12	Need for hemofiltration At 3 days Arm1: 1/150 (0.7) Arm2: 1/150 (0.7) Arm3: 2/150 (1.3) P=0.54	NR	Cardiogenic shock At 3 days Arm1: 8/150 (5.3) Arm2: 9/150 (6.0) Arm3: 6/150 (4.0) P=0.6 Recurrent MI At 3 days Arm1: 5/150 (3.3) Arm2: 6/150 (4.40) Arm3: 2/150 (1.3) P=0.30 Repeated urgent PCI At 3 days Arm1: 2/150 (1.3) Arm2: 5/150 (3.3) Arm3: 1/150 (0.7) P=0.66 Stroke At 3 days Arm1: 2/150 (1.3) Arm2: 2/150 (1.3) Arm3: 1/150 (1.3) P=1.0 MACE At 3 days Arm1: 15/150 (10) Arm2: 19/150 (12.7) Arm3: 11/150 (7.3) P=0.44

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Maioli, 2011[44] (continued)			Anterior MI At 3 days Arm1: 22/65 (33.8) Arm2: 16/63 (25.4) Arm3: 12/61 (19.7) P=0.07 LVEF <40% At 3 days Arm1: 24/61 (39.3) Arm2: 20/58 (34.5) Arm3: 12/56 (21.4) P=0.04 Volume contrast to eGFR ratio >3.7 At 3 days Arm1: 15/50 (30.0) Arm2: 15/55 (27.3) Arm3: 9/48 (18.8) p=0.20				
Manari, 2014[45]	Arm1: IV Normal Saline Arm2: High-dose IV Normal Saline Arm3: IV NaHCO3 Arm4: High-dose IV NaHCO3	SrCr ≥ 25% At 72 hours Arm1: 29/151 (19.2) Arm2: 27/145 (19) Arm3: 24/145 (16.6) Ar,4: 27/154 (17.5) p=0.92 SrCr >0.5mg/dl At 72 hours Arm1: 7/151 (4.6) Arm2: 8/142 (5.6) Arm3: 5/145 (3.4) Arm4: 3/154 (3.2) p=0.51	NR	NR	Time point NR Arm1: 0/151 (0) Arm2: 0/142 (0) Arm3: 0/145 (0) Arm4: 0/154 (0) p=NR	NR	NR

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Marron, 2007[48]	Arm1:IV Normal Saline Arm2: IV 0.45% Saline	SrCr ≥ 25% At 24 hours Arm1: 5 (13.5) Arm2: 4 (11.7) p=NS At 48 hours Arm1: 3 (8.1) Arm2: 1 (2.9) p=NS	NR	NR	NR	NR	NR
Mueller, 2002[49]	Arm1: IV Normal Saline Arm2: IV 0.45% Saline + 5% glucose	SrCr >0.5mg/dl At 48 hours Arm1: 0/26 (0) Arm2: 4/37 (11) p=0.04	StCr >0.5mg/dl At 48 hours Men At 48 hours Arm1: 4/507 (.8) Arm2: 5/522 (1) p=0.77 Women At 48 hours Arm1: 1/178 (.6) Arm2: 9/176 (5.1) p=0.01 Diabetes At 48 hours Arm1: 0/107 (0) Arm2: 6/110 (5.5) p=0.01 No diabetes At 48 hours Arm1: 5/578 (.9) Arm2: 8/588 (1.4) p=0.42	NR	NR	Arm1: 4.8 Arm2: 4.8 p=0.87	Major adverse cardiac event At 30 days Arm1: 14 (5.3) Arm2: 17 (6.4) p=0.59

Evidence Table I-21. Summary of the outcomes of studies comparing fluid strategies for the prevention of contrast-induced nephropathy and other outcomes (continued)

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days (SD)	Cardiac events, n/N (%)
Trivedi, 2003[63]	Arm1: Oral hydration Arm2: IV Normal Saline	SrCr >0.5mg/dl At 48 hours Arm1: 9/26 (34.6) Arm2: 1/27 (3.7) p=0.005	NR	NR	Need for dialysis At 48 hours Arm1: 0/26 (0) Arm2: 0/27 (0) p=NR	NR	NR

CIN=contrast induced nephropathy; CrCl=creatinine clearance; eGFR=estimated glomular filtration rate; IV=intravenous; LVEF=left ventricular ejection fraction; MACE=major adverse cardiac events; MI=myocardial infarction; Normal Saline=normal saline; NR=not reported; PCI=percutaneous coronary intervention; RRT=renal replacement therapy; SD=standard deviation; SrCr=serum creatinine
* n/N refers to number of events divided by number at risk.

Evidence Table I-22. Adverse events in studies comparing fluid strategies for the prevention of contrast induced nephropathy and other outcomes.

Author, Year	Adverse events
Bader,2004[7]	NR
Brar, 2014[9]	Shortness of breath
Mueller, 2002[49]	Vascular complications, 13 cases in the control group and 12 cases in the treatment group
Chen, 2008[14]	Adverse events reported by CIN, non-CIN status; Many conditions listed have no known correlation with intervention. They include major bleeding, death secondary to stroke, mechanical ventilation, continuous veno-venous filtration
Cho, 2010[15]	Other: in-house mortality; 0 in all arms
Koc, 2012[31]	No adverse reactions besides CIN
Kong, 2012[32]	NR
Krasuski, 2003[35]	NR
Lawlor, 2007[37]	Other: adverse side effects to NAC or placebo; no adverse side effects related to treatment with NAC or placebo were reported; Acute renal failure; No patients developed acute renal failure that required dialysis following their angiograms
Maioli, 2011[44]	Other: Major bleeding, Arm1: 8 (5.3%), Arm2: 12 (8%), Arm3: 6 (4%), Stroke, 2 cases (1.3%) in each arm,
Manari, 2014[45]	NR
Marron, 2007[48]	NR
Trivedi, 2003[63]	Other: adverse effects of saline hydration, (Amongst patients with contrast-induced renal failure, hospitalization was prolonged in 3 patients in the control group and 1 patient in the treatment group)

CIN=contrast induced nephropathy; g/kg/day=gram per kilogram per day; NAC=N-acetylcysteine; NaCl=sodium chloride; NR=not reported

Evidence Table I-23. Summary of characteristics of studies comparing dopamine versus other interventions for the prevention of contrast-induced nephropathy and other outcomes

Author, year	Comparison	N	Population included	Age, range of means§	No. female (%)‡	Mean followup	CM Route	Definition of CIN*	Study limitations
Abizaid, 1999 [1]	0.45% Saline vs. Dopamine + 0.45% Saline vs. Aminophylline + 0.45% Saline	60	Cr ≥1.5 mg/dl	74-75	20 (33)	6 days	LOCM (Ioxaglate) IA	A1	M
Hans, 1998 [23]	Placebo + IV Normal Saline vs. Dopamine + Oral Normal Saline	55	Cr ≥1.4 mg/dL	71-75	6 (10)	4 days	LOCM (Iohexol) IA	A2	H

%=percent; CIN=contrast induced nephropathy; CM=contrast media; HOCM=high-osmolarity contrast media; IA=intrarterial; IVF=intravenous fluid; LOCM=low osmolarity contrast media; Mg/dl=milligram per deciliter; Mg/kg/hour=milligram per kilogram per hour; N=sample size; Ug/kg/min=microgram per kilogram per minute; vs.=versus; Cr=creatinine

* CIN definitions: rise in serum creatinine relative to baseline: ≥25% (A1); ≥0.5 mg/dl (A2); ≥25% or ≥0.5 mg/dl (A3); ≥50% (A4), B: >25% reduction in creatinine clearance
† Study limitations: L=low risk of bias; M=moderate risk of bias; H=high risk of bias
‡ Percent females in entire study population
§ Some studies only reported mean age per arm, not one mean for whole population. This column shows range of the means across all arms.

Evidence Table I-24. Summary of the outcomes of studies comparing dopamine versus other interventions for the prevention of contrast-induced nephropathy

Author, year	Comparison	Incidence of CIN, n/N (%)	Incidence of CIN: subgroups, n/N (%)*	Mortality, n/N (%)	Need for RRT, n/N (%)	Length of hospital stay, mean days	Cardiac events, n/N (%)
Abizaid, 1999 [1]	Arm1: 0.45% IV Saline Arm2: dopamine + 0.45% Saline Arm3: Aminophylline + 0.45% Saline	Cr ≥25% Time point: NR Arm1: 6/20 (30) Arm2: 10/20 (50) Arm3: 7/20 (35) p=0.60	NR	NR	Time point: NR Arm1: 0/20 (0) Arm2: 0/20 (0) Arm3: 1/20 (5) p=1.00	Arm1: 7.0 Arm2: 6.8 Arm3: 7.0 p=0.82	NR
Hans, 1998 [23]	Arm1: Placebo + IV Normal saline Arm2: Dopamine + IV Normal saline	Cr ≥0.5 mg/dl At 24 hours Arm1: 7/27 (25.9) Arm2: 0/28 (0) p=0.002 At 48 hours Arm1: 8/27 (28.6) Arm2: 2/28 (7.1) p=0.026 At 72 hours Arm1: 10/27 (27.0) Arm2: 4/28 (14.3) p=0.048 At 96 hours Arm1: 12/27 (44.4) Arm2: 5/28 (17.9) p=0.031	NR	NR	NR	NR	NR

ANP=Atrial natriuretic peptide; CIN=contrast induced nephropathy; Cr=creatinine; IABP=intra-aortic balloon pump; IV=intravenous; NR=not reported; RRT=renal replacement therapy; VT/VF= Ventricular fibrillation and or ventricular tachycardia
* n/N refers to number of events divided by number at risk.

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